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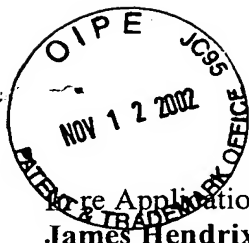
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Re Application of
James Hendrix et al

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Examiner:

Group Art Unit.: 1614

Application No.: 10/078,225

Filed: February 19, 2002

Title: **NOVEL HETEROCYCLIC
SUBSTITUTED CARBONYL
DERIVATIVES AND THEIR USE AS
DOPAMINE D3 RECEPTOR LIGANDS**

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I hereby certify that this paper (along with any referred to as being attached or enclosed) is being deposited with the United States Postal Service on the date shown below with sufficient postage as first class mail in an envelope addressed to the: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Date of Deposit November 7, 2002

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**SUBMISSION AND REQUEST FOR ENTRY
OF PRIORITY PAPERS 37 C.F.R. § 1.55(a)**

Dear Sir:

Applicants submit herewith certified copy of United Kingdom application(s), GB 0117577.7, filed on July 19, 2001, for which priority is claimed in the above-identified application.

This submission and request for entry is being made to satisfy the requirements under 35 U.S.C. § 119. Please note that no fees are associated with the entry of the priority documents since they are being timely submitted prior to the date the issue fee is due.

Respectfully submitted,

Barbara E. Kurys
Barbara E. Kurys, Reg. No. 34,650
Attorney/Agent for Applicant

Aventis Pharmaceuticals Inc.
Patent Department
Route #202-206 / P.O. Box 6800
Bridgewater, New Jersey 08807-0800
Telephone (908) 231-2965
Telefax (908) 231-2626

Aventis Docket No. A4015 US NP

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In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

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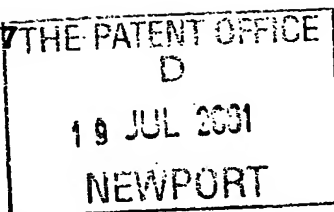


R. Mahoney

Signed

Dated 6 March 2002

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1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

19 JUL 2001

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

40/354/P/GB

2. Patent application number

(The Patent Office will fill in this part)

0117577.7

19 JUL 2001

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Aventis Pharmaceuticals Products Inc
Route 202-206
PO Box 6800
Bridgewater
New Jersey 08807-0800
USA

Patents ADP number (if you know it)

If the applicant is a corporate body, give the country/state of its incorporation

8018442001

4. Title of the invention

NOVEL HETEROCYCLIC SUBSTITUTED CARBONYL
DERIVATIVES AND THEIR USE AS DOPAMINE D₃
RECEPTOR LIGANDS

5. Name of your agent (if you have one)

Adamson Jones

"Address for service" in the United Kingdom
to which all correspondence should be sent
(including the postcode)

Broadway Business Centre
32a Stoney Street
Nottingham
NG1 1LL

Patents ADP number (if you know it)

7975907001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application number
(if you know it)

Date of filing
(day / month / year)

US

60/269,672

16/02/2001

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? (Answer 'Yes' if:

Yes

- a) any applicant named in part 3 is not an inventor, or
 - b) there is an inventor who is not named as an applicant, or
 - c) any named applicant is a corporate body.
- See note (d))

Patents Form 1/77

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Continuation sheets of this form

Description 156

Claim(s) 48

Abstract 1

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

11. I/We request the grant of a patent on the basis of this application.

Signature

Date

18 July 2001

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr S A Jones

0115 9247 147

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

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NOVEL HETEROCYCLIC SUBSTITUTED CARBONYL DERIVATIVES AND THEIR USE AS DOPAMINE D₃ RECEPTOR LIGANDS

BACKGROUND OF THE INVENTION

The subject invention relates to novel heterocyclic derivatives that selectively bind to the dopamine D₃ receptor. The therapeutic effect of currently available antipsychotic agents (neuroleptics) is generally believed to be exerted via blockade of D₂ receptors; however this mechanism is also thought to be responsible for undesirable extrapyramidal side effects (eps) associated with many neuroleptic agents. Without wishing to be bound by theory, it has been suggested that blockade of the dopamine D₃ receptor may give rise to beneficial antipsychotic activity without significant eps. (see for example Sokoloff et al, *Nature*, 1990; 347: 146-151; and Schwartz et al, *Clinical Neuropharmacology*, Vol 16, No. 4, 295-314, 1993). This receptor is shown in high abundance in brain regions associated with emotional and cognitive functions. Compounds that selectively bind to the dopamine D₃ receptor are useful in treating certain central nervous system disorders. These central nervous system disorders include the following indications:

- 1) Psychoses (including schizophrenia) – See, for example, *Biochem Pharmacol*, 1992, 3(4), 659-66; *Clin Neuropharmacol*, 1993, 16(4), 295-314; *Neuropsychopharmacology*, 1997, 16(6), 375-84; *Am J Psychiatry*, 1999, 156(4), 610-616; *Psychopharmacology (Berl)*, 1995, 120(1), 67-74.
- 2) Substance dependence and substance abuse – See, for example, *Neuroreport*, 1997, 8(9-10), 2373-2377; *J Pharmacol Exp Ther*, 1996, 278(3), 1128-37; *Brain Res Mol Brain Res*, 1997, 45(2), 335-9.
- 3) Mood Disorders (including mania, depressive disorders and bipolar disorders) – See, for example, *Clin Neuropharmacol*, 1998, 21(3), 176-80; *Am J Med Genet*, 1998, 81(2), 192-4; *J Clin Psychiatry*, 1995, 56(11), 514-518; *J Clin Psychiatry*, 1995, 56(9), 423-429; *Am J Med*

Genet, 1995, 60(3), 234-237; *Pharmacopsychiatry*, 1999, 32(4), 127-135; *J Affect Disord*, 1999, 52(1-3), 275-290; *Am J Psychiatry*, 1999, 156(4), 610-616.

4) dyskinetic disorders (including Parkinson's Disease, Parkinsonism, Neuroleptic-Induced Tardive Dyskinesia and Gilles de la Tourette Syndrome) – See, for example, *Clin Neuropharmacol*, 2000, 23(1), 34-44; *Eur J Pharmacol*, 1999, 385(1), 39-46.

5) sleep disorders (including narcolepsy) - The D₃ agonist pramipexole causes narcolepsy. A D₃ antagonist would be useful for reversing this undesirable side effect. See *Aust Fam Physician*, 1999, 28(7), 737; *Neurology*, 1999, 52(9), 1908-1910.

6) anxiety disorders (including obsessive compulsive disorders) – See, for example, *Physiol Behav*, 1997, 63(1), 137-141; *J Clin Psychiatry*, 1995, 56(9), 423-429; *J Psychiatry Neurosci*, 2000, 25(2), 185; *J Affect Disord*, 1999, 56(2-3), 219-226.

7) nausea - Dopamine antagonists are used alone and in combination with 5HT₃ antagonists. See, for example, *Support Care Cancer*, 1998, 6(1), 8-12; *Support Care Cancer*, 2000, 8(3), 233-237; *Eur J Anaesthesiol*, 1999, 16(5), 304-307.

8) dementia – See, for example, *Behav Brain Res*, 2000, 109(1), 99-111; *Neuroscience*, 1999, 89(3), 743-749.

SUMMARY OF THE INVENTION

This invention relates to a class of compounds and pharmaceutically acceptable salts thereof which are selective modulators of dopamine D₃ receptors. The compounds may act as agonists, partial agonists, antagonists or allosteric modulators of dopamine D₃ receptors, and are useful for a variety of therapeutic applications.

In another aspect, the invention relates to a method for treating central nervous system disorders associated with the dopamine D₃ receptor activity in a patient in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound described herein for alleviation of such disorder. The central nervous system conditions or disorders that may be treated with these compounds include Psychotic Disorders, Substance Dependence, Substance Abuse, Dyskinetic Disorders (e.g. Parkinson's Disease, Parkinsonism, Neuroleptic-Induced Tardive Dyskinesia, Gilles de la Tourette Syndrome and Huntington's Disease), Nausea, Dementia, Anxiety Disorders, Sleep

Disorders, Circadian Rhythm Disorders and Mood Disorders.

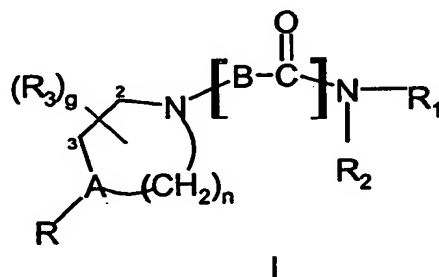
In yet another aspect, the subject invention is directed toward a pharmaceutical composition comprising an effective amount of a compound described herein with a pharmaceutically-acceptable carrier or diluent optionally in conjunction with one or more dopamine D₁, D₂, D₄, D₅ or 5HT receptor antagonists.

In yet another aspect, the subject invention is directed towards processes for the preparation of the class of compounds described herein.

Also within the scope of this invention are methods for using these novel compounds as imaging agents for dopamine D₃ receptors. Methods of using these compounds as imaging agents are presented, as are intermediates and methods for making the imaging agents.

DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there are provided compounds of formula I



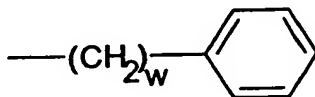
wherein

A is CH or N;

n is 2 or 3;

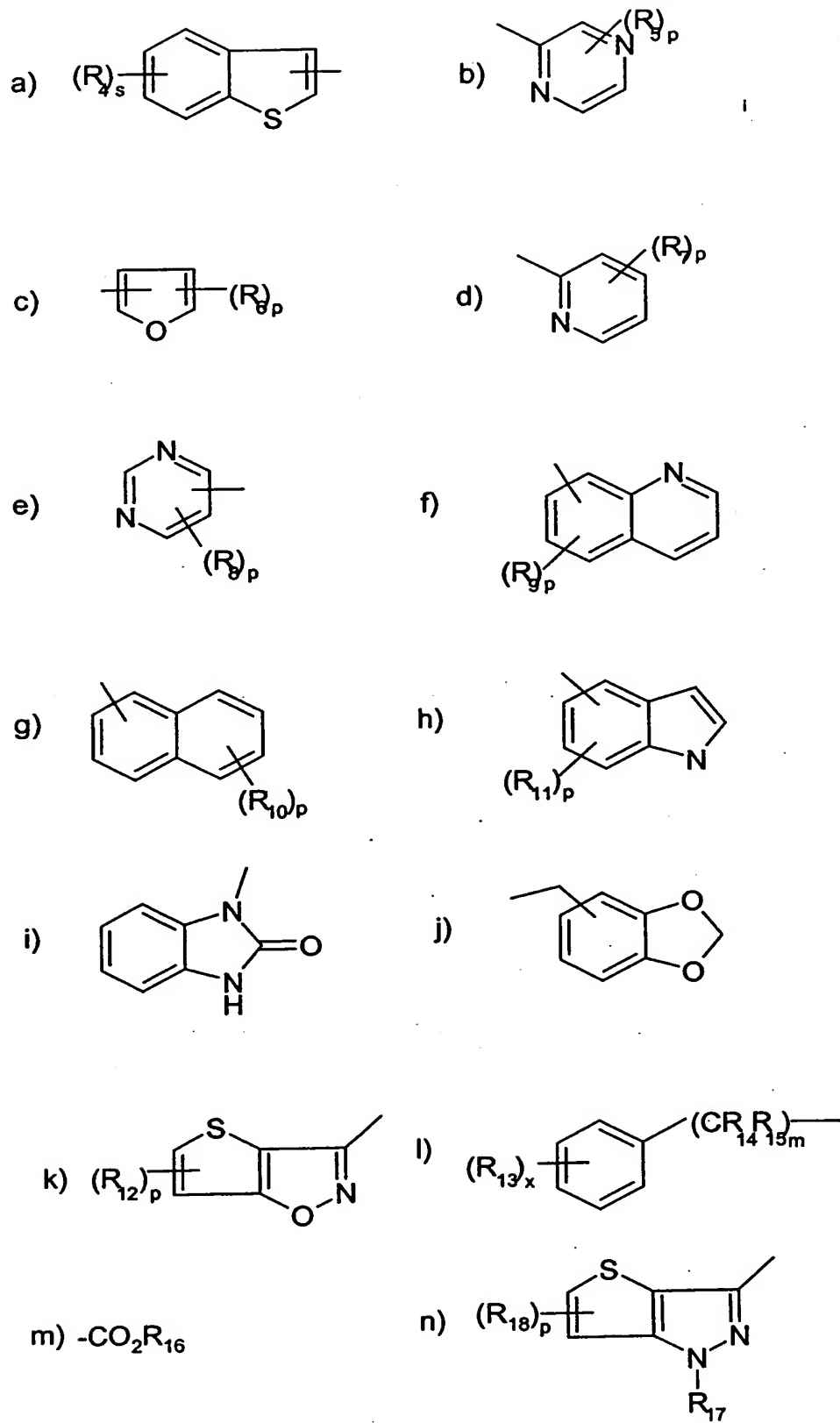
g is 1 or 2;

each R₃ is independently hydrogen, C₁-C₆alkyl, or



wherein w is 1, 2, or 3;

R is selected from the group consisting of (a) - (n):



wherein

each $R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}$ and R_{18} is independently hydrogen, C_1 - C_6 alkyl, halogen, trifluoromethyl or $-CH_2OC_1$ - C_6 alkyl;

p, s and x are 0, 1, or 2;

each R_{13} is independently hydrogen, C_1 - C_6 alkyl, halogen, trifluoromethyl, C_1 - C_6 alkoxy, nitro, CN, or COC_1 - C_6 alkyl;

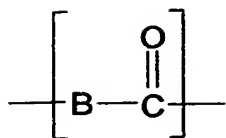
R_{16} is C_1 - C_6 alkyl;

each R_{14} and R_{15} is independently hydrogen or C_1 - C_6 alkyl;

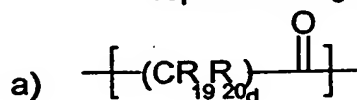
R_{17} is hydrogen, C_1 - C_6 alkyl, Ar, $-COAr$, $-CONHAr$ or $-SO_2-Ar$ wherein

Ar is a phenyl group which is unsubstituted or mono- or di-substituted with substituents independently selected from C_1 - C_6 alkyl, halogen, trifluoromethyl, C_1 - C_6 alkoxy, nitro, CN and COC_1 - C_6 alkyl; and

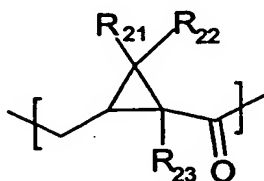
m is 0, 1, or 2;



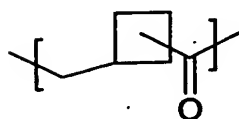
represents a group selected from (a) - (e):



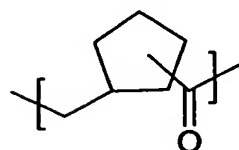
b)

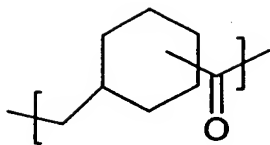


(c)



(d)





wherein

each R_{19} and R_{20} is independently hydrogen, hydroxy or C_1 - C_6 alkyl;

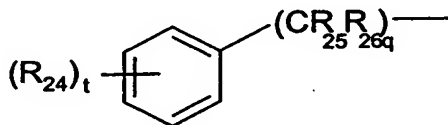
R_{21} , R_{22} , and R_{23} are each independently hydrogen or C_1 - C_3 linear alkyl; and

d is 3 or 4;

R_1 is a) hydrogen;

b) C_1 - C_6 alkyl, unsubstituted or mono- or di-substituted with hydroxy; or

c)



wherein

each R_{24} is independently hydrogen or C_1 - C_6 alkyl;

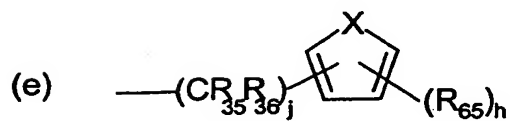
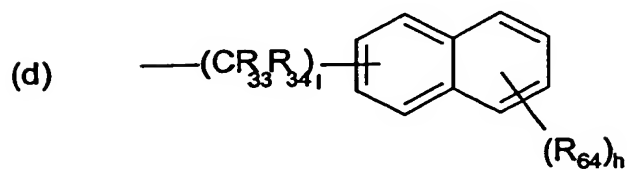
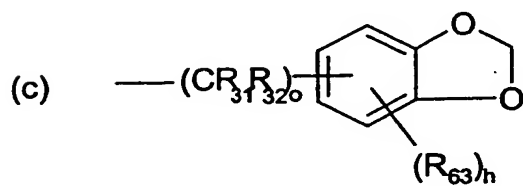
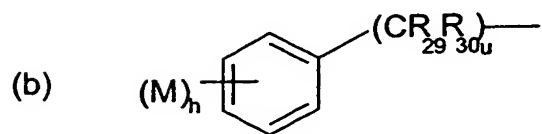
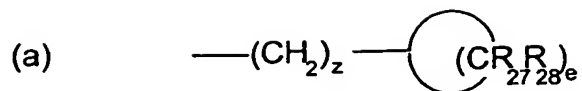
each R_{25} , and R_{26} is independently hydrogen or

C_1 - C_6 alkyl;

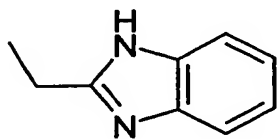
t is 0 or 1; and

q is 0 or 1;

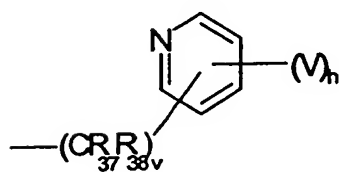
R_2 is a group selected from (a) – (n):



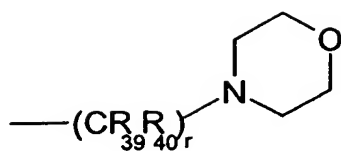
(f)



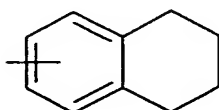
(g)



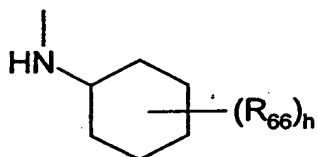
(h)



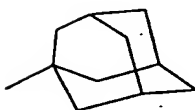
(i)



(j)



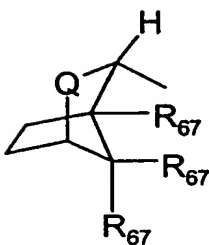
(k)



(l)



(m)



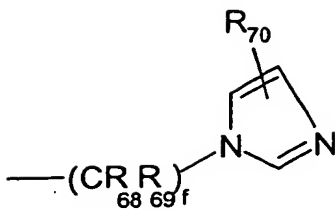
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15

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(n)



wherein

each R_{27} and R_{28} is independently selected from:

- (1) hydrogen;
- (2) C_1 - C_6 alkyl;
- (3) C_1 - C_6 alkoxy;
- (4) $-\text{CO}_2\text{-}R_{43}$ wherein R_{43} is hydrogen or C_1 - C_2 alkyl;
- (5) hydroxy;
- (6) $-(\text{CH}_2)\text{-OR}_{44}$ wherein R_{44} is hydrogen or C_1 - C_2 alkyl;
- (7) $-(\text{CO})\text{-NR}_{45}R_{46}$ wherein R_{45} and R_{46} are each independently hydrogen, C_1 - C_2 alkyl, or R_{45} and R_{46} taken together form a 5-membered monocyclic ring;
- (8) $-(\text{CH}_2)_a\text{-OR}_{47}$ wherein R_{47} is hydrogen or C_1 - C_2 alkyl and a is 1 or 2;

each M and V is a group independently selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, trifluoromethyl, hydroxy, phenoxy or

$-\text{NR}_{48}R_{49}$ wherein R_{48} and R_{49} are each independently hydrogen or C_1 - C_2 alkyl;

each R_{29} , R_{30} , R_{31} , R_{32} , R_{33} , R_{34} , R_{35} , R_{36} , R_{37} , R_{38} , R_{39} , R_{40} , R_{68} , and R_{69} is independently hydrogen or C_1 - C_6 alkyl;

each R_{63} , R_{64} and R_{65} is independently hydrogen, halogen, C_1 - C_6 alkyl or C_1 - C_6 alkoxy;

each R_{66} is independently hydrogen, hydroxy, C_1 - C_6 alkyl or C_1 - C_6 alkoxy;

Q is CH_2 , CHOH or C=O ;

each R_{67} is independently hydrogen or C_1 - C_6 alkyl;

R_{70} is hydrogen, C_1 - C_6 alkyl, halogen, or a phenyl group which is unsubstituted or mono-substituted with C_1 - C_6 alkyl, halogen or trifluoromethyl;

f is 1, 2, 3, or 4;

z is 0 or 1;

u, j, l, o, r are 0 or 1;

h is 0, 1, 2, or 3;

e is 2, 3, 4, 5, or 7;

v is 0, 1 or 2; and

X is O or S;

or R_1 and R_2 are joined together to form a 5-, 6-, or 7-membered monocyclic saturated ring, and in which the ring is unsubstituted or mono- or di-substituted, the substituents independently selected from:

(1) C_1 - C_6 alkyl;

(2) $-\text{CO}_2-(C_1\text{-}C_2\text{alkyl})$;

(3) $-\text{NR}_{50}\text{R}_{51}$ wherein R_{50} and R_{51} are each independently C_1 - C_6 alkyl;

(4) hydroxy;

(5) $-(\text{CH}_2)\text{-OR}_{52}$ wherein R_{52} is hydrogen or C_1 - C_2 alkyl;

(6) $-\text{NR}_{54}\text{-COR}_{53}$ wherein R_{54} is hydrogen or C_1 - C_6 alkyl and R_{53} is hydrogen or C_1 - C_2 alkyl ;

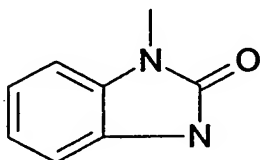
(7) $=\text{O}$;

(8) $-\text{CN}$;

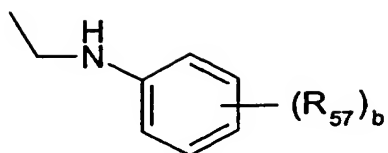
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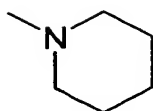
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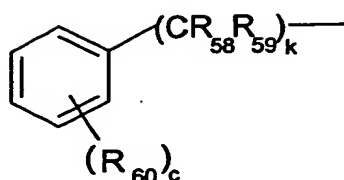
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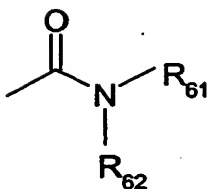
(12)



(13)



(14)



wherein

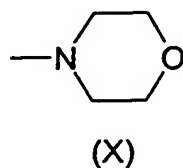
i is 0 or 1;

each R_{55} , R_{56} , R_{58} , and R_{59} is independently hydrogen or C_1 - C_6 alkyl;each R_{57} is independently hydrogen, halogen or C_1 - C_6 alkyl;each R_{60} is independently hydrogen, halogen or C_1 - C_6 alkyl; R_{61} and R_{62} are each independently hydrogen or C_1 - C_6 alkyl;

k is 0 or 1;

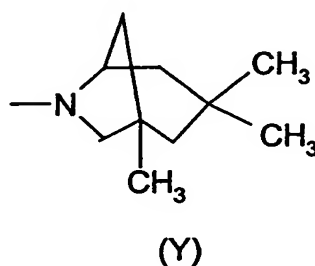
b and c are 0, 1 or 2;

or R_1 and R_2 are joined together to form a group of formula X;



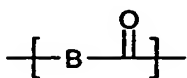
5

or R_1 and R_2 are joined together to form the group of formula (Y)



with the proviso that, when n is 2, R_3 is hydrogen or C_1 - C_6 alkyl,

10



is a group of formula (a), and R is a group of formula:

15

(a) wherein R_4 is hydrogen, halogen or C_1 - C_6 alkyl, and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

(a) wherein z is 0,

(b) wherein u is 0 and M is hydrogen, halogen, C_1 - C_6 alkyl, or trifluoromethyl,

(c) wherein o is 0,

(d) wherein l is 0,

(e) wherein j is 0,

(g) wherein v is 0, or

20

(i);

and also when R is the group of formula (a), R_1 and R_2 cannot be joined together to form the group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

25

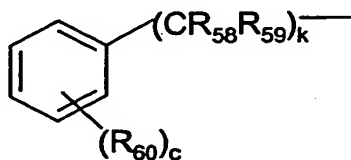
wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl;

(b) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
- (b),
- (c) wherein o is 0,
- (d) wherein l is 0,
- (i),
- (k),
- (l), or
- (m) wherein Q is CH_2 ;

and also when R is the group of formula (b), R_1 and R_2 cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl or



(c) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

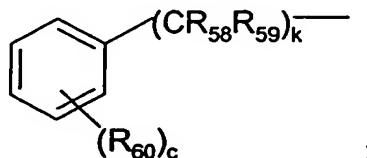
- (c) wherein o is 0,
- (d) wherein l is 0, or
- (i);

(d) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
- (b) wherein u is 1,
- (c) wherein o is 0,
- (d),
- (i),
- (k),
- (l), or
- (m) wherein Q is CH_2 ;

and also when R is the group of formula (d), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

5 wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or



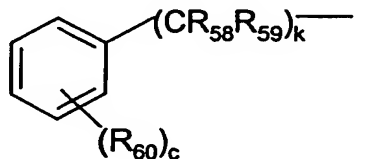
(e) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

10

- (a),
- (b),
- (c) wherein o is 0,
- (d),
- 15 (i),
- (k),
- (l), or
- (m) wherein Q is CH₂;

20 and also when R is the group of formula (e), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

 wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or



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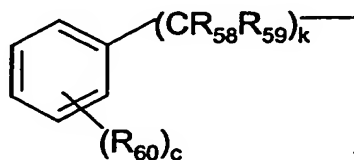
(f) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

- (a),
- 30 (b),
- (c) wherein o is 0,

- (d),
 (i),
 (k),
 (l), or
 (m) wherein Q is CH₂;

and also when R is the group of formula (f), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or

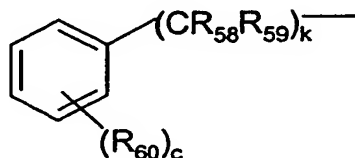


(g) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

- (a),
 (b) wherein u is 1,
 (c) wherein o is 0,
 (d),
 (i),
 (k),
 (l), or
 (m) wherein Q is CH₂;

and also when R is the group of formula (g), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or

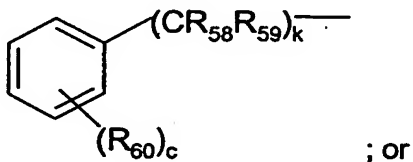


(h) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
 (b),
 (c) wherein o is 0,
 (d),
 (i),
 (k),
 (l), or
 (m) wherein Q is CH_2 ;

and also when R is the group of formula (h), R_1 and R_2 cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl or



- (j) then R_1 and R_2 cannot be joined together to form a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring
 wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl.

The subject invention is directed toward compounds or pharmaceutically acceptable salts of Formula I as depicted above in either racemic or pure stereoisomeric forms.

Terms used herein have the following meanings:

a) "Pharmaceutically acceptable salts" means either an acid addition salt or a basic addition salt which is compatible with the treatment of patients for the intended use.

"Pharmaceutically acceptable acid addition salt" is any non-toxic organic or inorganic acid addition salt of the base compounds represented by Formula I or any of its intermediates. Illustrative inorganic acids which form suitable salts include hydrochloric, hydrobromic, sulfuric and phosphoric acid and acid metal salts such as sodium monohydrogen

orthophosphate and potassium hydrogen sulfate. Illustrative organic acids which form suitable salts include the mono-, di- and tri-carboxylic acids. Illustrative of such acids are, for example, acetic, glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic, hydroxybenzoic, phenylacetic, cinnamic, salicylic, 2-phenoxybenzoic, p-toluenesulfonic acid and sulfonic acids such as methanesulfonic acid and 2-hydroxyethanesulfonic acid. Either the mono- or di-acid salts can be formed, and such salts can exist in either a hydrated, solvated or substantially anhydrous form. In general, the acid addition salts of these compounds are more soluble in water and various hydrophilic organic solvents and which in comparison to their free base forms, generally demonstrate higher melting points.

"Pharmaceutically acceptable basic addition salts" means non-toxic organic or inorganic basic addition salts of the compounds of Formula (I) or any of its intermediates. Examples are alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, trimethylamine and picoline. The selection criteria for the appropriate salt will be known to one skilled in the art.

b) "Stereoisomers" is a general term for all isomers of the individual molecules that differ only in the orientation of their atoms in space. It includes mirror image isomers (enantiomers), geometric (cis/trans) isomers, and isomers of compounds with more than one chiral center that are not mirror images of one another (diastereoisomers).

c) "Alkyl" means a branched or straight chain alkyl or alkylene group, as is appropriate to the formula, specified by the amount of carbons in the alkyl, e.g., C₁-C₈ alkyl means a one, two, three, four, five or six carbon branched or straight chain alkyl or alkylene, as the case may be, or any ranges thereof, for example, but not limited to, C₁-2, C₁-3, C₁-4, C₁-5, C₂-3, C₂-4, C₂-5, C₂-6, C₃-4, C₃-5, C₃-6, C₄-5, C₄-6, C₅-6, etc.

d) "Patient" means a warm blooded animal, such as for example rat, mice, dogs, cats, guinea pigs, and primates such as humans.

e) "Treat" or "treating" means to alleviate symptoms, eliminate the causation of the symptoms either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder or condition.

f) "Therapeutically effective amount" means a quantity of the compound which is

effective in treating the named disorder or condition.

- g) "Pharmaceutically acceptable carrier" is a non-toxic solvent, dispersant, excipient, adjuvant or other material which is mixed with the active ingredient in order to permit the formation of a pharmaceutical composition, i.e., a dosage form capable of administration to the patient. One example of such a carrier is a pharmaceutically acceptable oil typically used for parenteral administration.
- h) "Psychoses" or "Psychotic Disorders" means conditions wherein the patient experiences a major mental disorder of organic and/or emotional origin characterized by derangement of the personality and loss of contact with reality, often with delusions, hallucinations or illusions. Included under the term psychoses are the disorders schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder not otherwise specified, and substance-induced psychotic disorder, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., published 1994 by the American Psychiatric Association, Washington D.C. USA, incorporated herein by reference.
- i) "Substance Dependence" means a condition wherein the patient exhibits a maladaptive pattern of substance use, leading to clinically significant impairment or distress. There is a pattern of repeated self-administration that usually results in tolerance, withdrawal, and compulsive drug-taking.
- j) "Substance Abuse" means a condition wherein the patient exhibits a maladaptive pattern of substance use manifested by recurrent and significant adverse consequences related to the repeated use of substances. There may be repeated failure to fulfill major role obligations, repeated use in situations in which it is physically hazardous, multiple legal problems, and recurrent social and interpersonal problems. Unlike the criteria for Substance Dependence, the criteria for Substance Abuse do not include tolerance, withdrawal, or a pattern of compulsive use and instead only include the harmful consequences of repeated use.
- k) "Parkinson's Disease" means a slowly progressive neurological condition, characterized by tremor, rigidity, bradykinesia, and postural instability. Other manifestations include depression and dementia.
- l) "Parkinsonism" means a condition where the patient exhibits Parkinsonian signs or

symptoms (i.e. tremor, muscular rigidity, or akinesia) that develop in association with the use of neuroleptic medication.

m) "Neuroleptic-Induced Tardive Dyskinesia" means a disorder characterized by involuntary movements of the tongue, jaw, trunk, or extremities which have developed in association with the use of neuroleptic medication. The involuntary movements may be choreiform, athetoid or rhythmic.

n) "Gilles de la Tourette Syndrome" means a condition manifested by motor and vocal tics. (A tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization.) The disturbance causes marked distress or significant impairment in social, occupational, or other important areas of functioning. The onset is before age eighteen years and the disturbance is not due to the physiological effects of a substance or general medical condition.

o) "Dementia" means disorders characterized by the development of multiple cognitive deficits that include memory impairment and are due to the direct physiological effects of a general medical condition, to the persisting effects of a substance, or to multiple etiologies (e.g., the combined effects of cerebrovascular disease and Alzheimer's disease). Memory impairment is required to make the diagnosis of a dementia and is a prominent early symptom. Dementia disorders share a common symptom presentation but are differentiated based on etiology. See Diagnostic and Statistical Manual of Mental Disorders, 4th ed., American Psychiatric Association, for diagnostic criteria.

p) "Anxiety Disorders" means disorders that include Panic Disorder Without Agoraphobia, Panic Disorder with Agoraphobia, Agoraphobia Without History of Panic Disorder, Specific Phobia, Social Phobia, Obsessive-Compulsive Disorder, Post-traumatic Stress Disorder, Acute Stress Disorder, Generalized Anxiety Disorder, Anxiety Disorder Due to a General Medical Condition, Substance-Induced Anxiety Disorder, and Anxiety Disorder Not Otherwise Specified, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th ed.

q) "Sleep Disorders" means disorders that include Primary Sleep Disorders, Sleep Disorder Related to Another Mental Disorder, Sleep Disorder Due to a General Medical Condition, and Substance-Induced Sleep Disorder as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Primary Sleep Disorders are those in which none of the etiologies listed below (i.e., another mental disorder, a general medical condition,

or a substance) is responsible. Primary Sleep Disorders are presumed to arise from endogenous abnormalities in sleep-wake generating or timing mechanisms, often complicated by conditioning factors. Primary Sleep Disorders in turn are subdivided into Dyssomnias (characterized by abnormalities in the amount, quality, or timing of sleep) and Parasomnias (characterized by abnormal behavioral or physiological events occurring in association with sleep, specific sleep stages, or sleep-wake transitions). A representative example of a Primary Sleep Disorder is Narcolepsy. Narcolepsy is characterized by repeated irresistible attacks of refreshing sleep, cataplexy, and recurrent intrusions of elements of rapid eye movement (REM) sleep into the transition period between sleep and wakefulness.

r) "Mood Disorders" are disorders that have a disturbance in mood as the predominant feature. As defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Mood Disorders are divided into the Depressive Disorders ("unipolar depression"), the Bipolar Disorders, and two disorders based on etiology – Mood Disorder Due to a General Medical Condition and Substance-Induced Mood Disorder. The Depressive Disorders (i.e., Major Depressive Disorder, Dysthymic Disorder, and Depressive Disorder Not Otherwise Specified) are distinguished from the Bipolar Disorders by the fact that there is no history of ever having had a Manic, Mixed, or Hypomanic Episode. The Bipolar Disorders (i.e., Bipolar I Disorder, Bipolar II Disorder, Cyclothymic Disorder, and Bipolar Disorder Not Otherwise Specified) involve the presence (or history) of Manic Episodes, Mixed Episodes, or Hypomanic Episodes, usually accompanied by the presence (or history) of Major Depressive Episodes.

s) "Circadian Rhythm Disorder" means a persistent or recurrent pattern of sleep disruption leading to excessive sleepiness or insomnia that is due to a mismatch between the sleep-wake schedule required by a person's environment and his or her circadian sleep-wake pattern. The sleep disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance does not occur exclusively during the course of another Sleep Disorder or other mental disorder. The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.

Preferred compounds are those wherein R is group (a) or group (k). When R is group (a), R₄ is further preferred to be halogen or CF₃. When R is group (k), R₁₂ is further preferred to be hydrogen, C₁-C₆alkyl, or -CH₂OC₁-C₆alkyl. R₂ is preferred to be group (a), (b) or (n). When R₂ is group (a), z is further preferred to be 0 or 1; e is further preferred to be 5; and each R₂₇ and R₂₈ is further preferred to be independently selected from hydrogen or C₁-C₆alkyl. When R₂ is group (b), M is further preferred to be hydrogen, C₁-C₆alkoxy or C₁-C₆alkyl and u is

further preferred to be 0 or 1. When R_2 is group (n), R_{70} is further preferred to be hydrogen and f is further preferred to be 3.

Specific embodiments of the invention include the compounds set forth in the tables herein.

5

Preferred embodiments of the invention are those compounds of Formula I set forth in Table 1 that exhibit enhanced D3 potency. Particularly preferred compounds include the following:

10

2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-*trans*-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide

2-[4-(2,4-Dimethyl-phenyl)-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide

15

2-[4-(Chloro-trifluoromethyl-pyridin-2-yl)-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide

2-[4-(2,5-Dimethyl-phenyl)-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide

20

2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-methyl-cyclohexyl)-amide

25

2-(4-Thieno[2,3-*d*]isoxazol-3-yl-piperidin-1-ylmethyl)-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-methyl-cyclohexyl)-amide

2-[4-*o*-Tolyl-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide

30

4-[4-(6-Fluoro-benzo[b]thiophen-3-yl)-piperazin-1-yl]-*N*-(*trans*-4-methyl-cyclohexyl)-butyramide

2-(4-Thieno[2,3-*d*]isoxazol-3-yl-piperidin-1-ylmethyl)-(2R, 3R)-cyclopropanecarboxylic acid (3-imidazol-1-yl-propyl)-amide

35

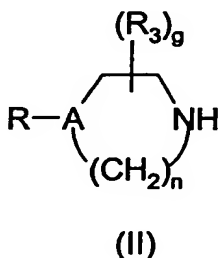
2-(4-Thieno[2,3-*d*]isoxazol-3-yl-piperazin-1-ylmethyl)-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-methyl-cyclohexyl)-amide

The compounds of the present invention may be prepared by various methods. Schemes I through VI show the different ways of preparing the compounds of Formula I.

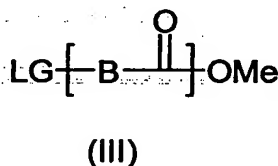
The compounds of formula (I) of this invention can be synthesized by following or combining one or more of the steps described below, not necessarily in the order presented. Throughout the description of the synthetic steps, the definitions of R, R₁, R₂, R₃, g, n, B and A are as given above unless otherwise stated or indicated, and other nomenclatures appearing below shall have the same meanings defined in their respective first appearances unless otherwise stated or indicated.

Compounds of the present invention may be prepared according to a process which comprises

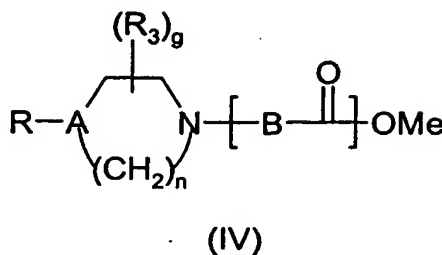
(a) reacting a compound of formula (II):



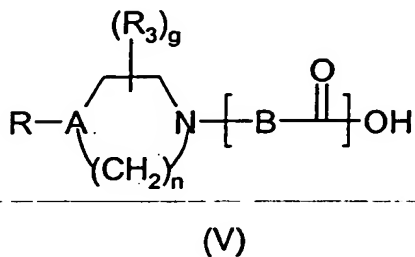
with a compound of formula (III) wherein "LG" is a suitable leaving group selected from chlorine, bromine, iodine, mesyl, tosyl, brosyl, triflyl, nosyl, nonaflyl or tresyl:



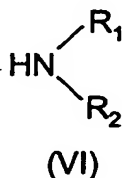
to provide a compound of formula (IV):



(b) hydrolyzing a compound of formula (IV) to provide a compound of formula (V):



5 (c) reacting a compound of formula (V) with a compound of formula (VI):



to provide a compound of formula (I).

10

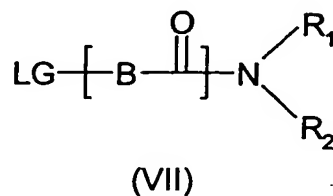
Typically, the reaction in step (a) is carried out in polar solvent such as, for example, acetonitrile and an amine base such as, for example, triethylamine. The reaction is typically conducted at a temperature of about 80 °C to about 85 °C for about 1 to 3 hours.

15 The reaction in step (b) is typically carried out in a water miscible solvent such as, for example, methanol or 1,4-dioxane in the presence of an aqueous hydroxide base such as, for example, 5 N sodium hydroxide. The reaction is typically carried out at a temperature of about 55 °C to about 65 °C for about 2 to 3 hours.

20 The reaction in step (c) is typically carried out in a polar solvent such as, for example, N,N'-dimethylformamide, in the presence of a weak base such as, for example, N-methylmorpholine with a suitable coupling reagent. A suitable coupling reagent is, for example, DCC (1,3-dicyclohexylcarbodiimide), EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) or TOTU {O-[(ethoxycarbonyl)cyanomethyleneamino]-N,N,N',N'-tetramethyluronium tetrafluoroborate}. Typically, the reaction takes place at a temperature of
 25 about 20 °C to about 25 °C for about 16 to 20 hours.

Alternatively, compounds of the present invention may be prepared according to a process which comprises:

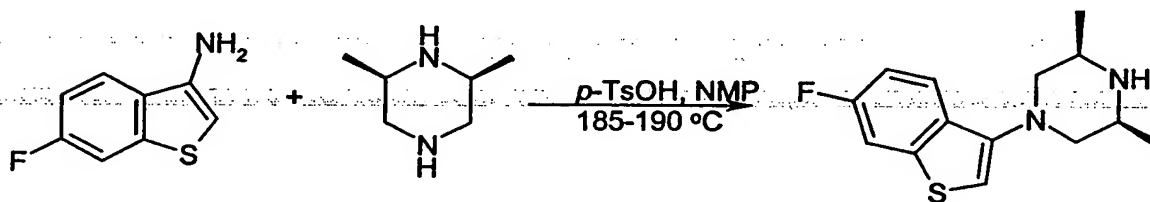
- (a) reacting a compound of formula (VII) wherein "LG" is a suitable leaving group selected from chlorine, bromine, iodine, mesyl, tosyl, brosyl, triflyl, nosyl, nonafllyl or tresyl:



with a compound of formula (II) to provide a compound of formula (I). This reaction is typically carried out in a polar solvent and an amine base such as acetonitrile and triethylamine, at a temperature of about 55 °C to about 65 °C for about 16 to 20 hours.

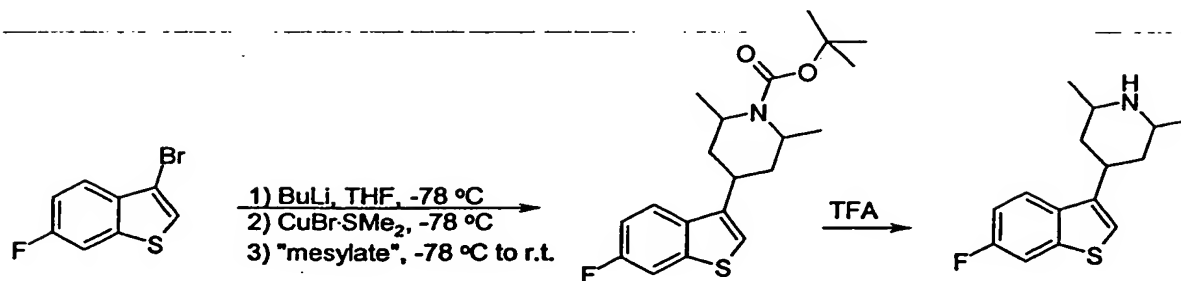
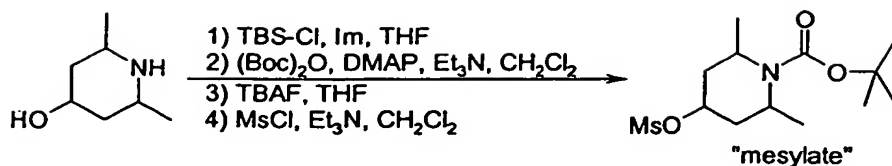
- Compounds of formula (II) are either commercially available or may be prepared via synthetic methods well known in the art. For example, Scheme I describes the coupling of a benzthiophene with a commercially-available substituted piperazine. The synthesis is analogous for the un-substituted piperazine analogs. The less sterically hindered piperazine nitrogen is more reactive and cleanly gives a single product in the benzo[b]thiophene coupling. The more sterically hindered nitrogen can then be alkylated as before in the un-substituted piperazines.

SCHEME I

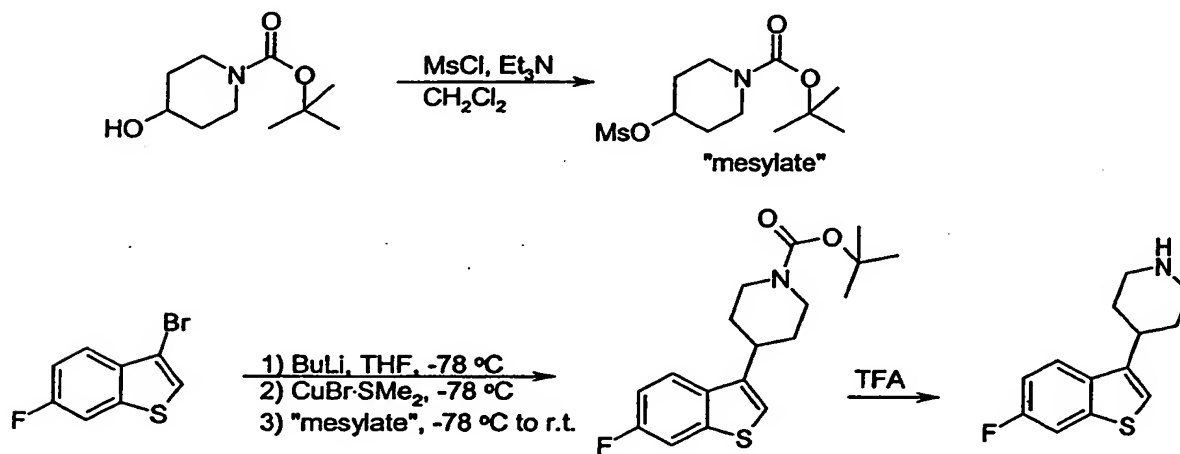


Piperidine-substituted compounds may be prepared via syntheses analogous to those shown in the following reaction Schemes II and III.

SCHEME II

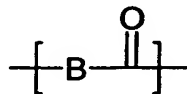


SCHEME III



The preparation of various substituted aza- and diazacycloheptanes is described by Treiber et al. in WO 9725324.

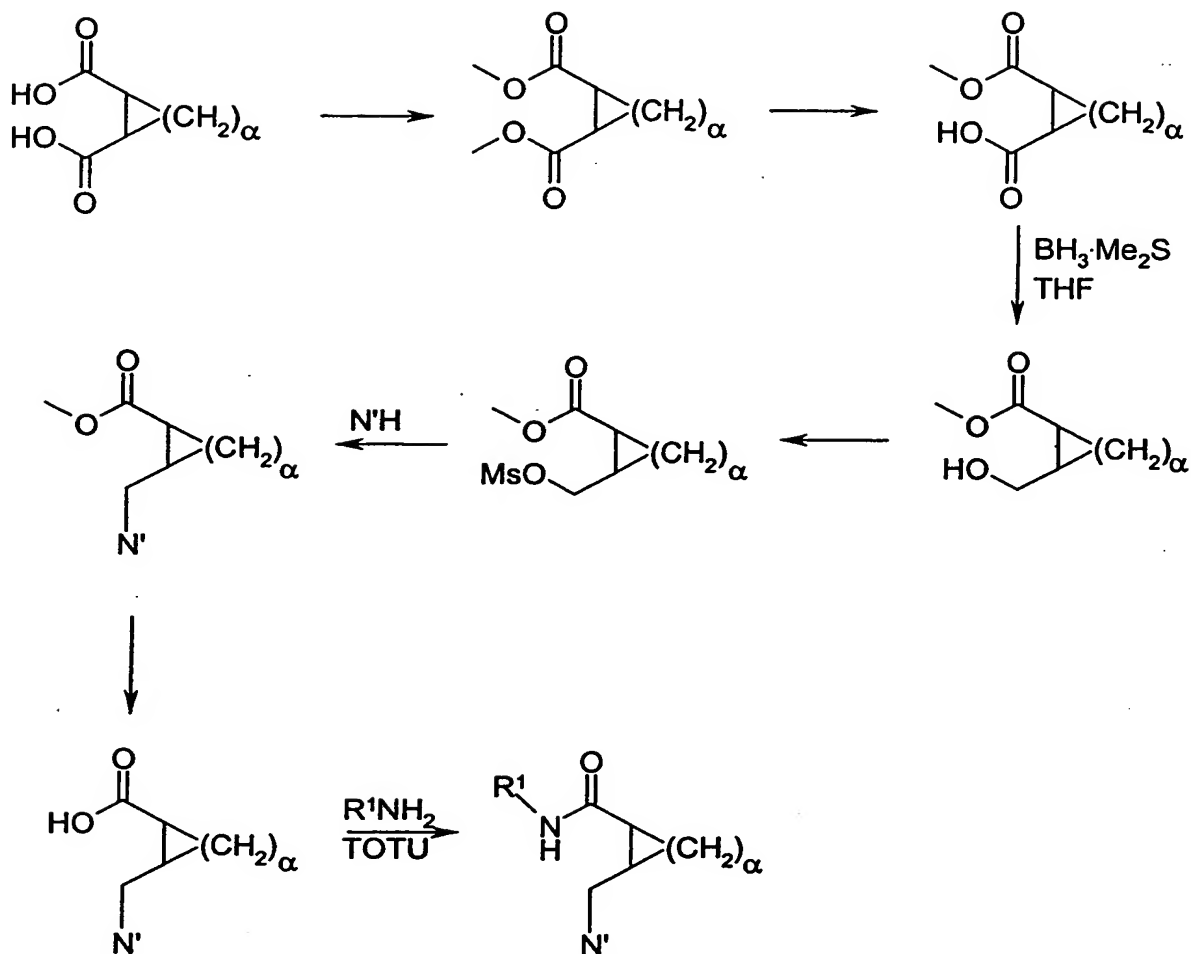
10 The synthesis of compounds of formula (I) wherein the variable designated as



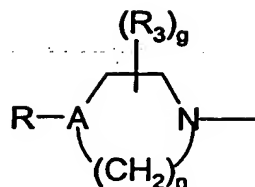
contains a carbocycle is shown in general reaction Scheme IV. For the sake of simplification, the description of synthetic schemes is presented below for compounds which contain this carbocyclic group, but it will be apparent that compounds which do not contain a carbocyclic group can be prepared by utilizing the synthetic schemes and making necessary modifications.

15

Scheme IV



5 α is 1, 2, 3 or 4; and N' - is

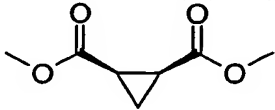
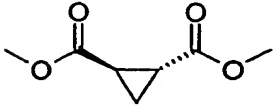
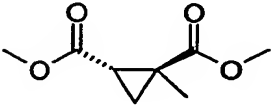
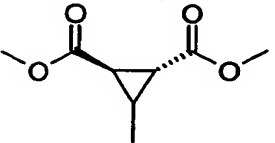
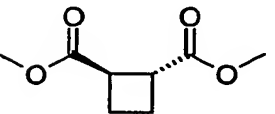
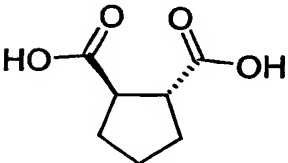
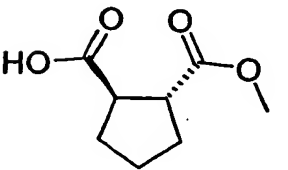
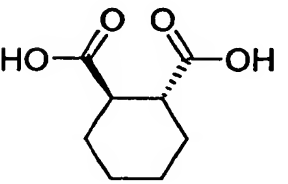
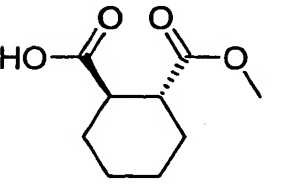


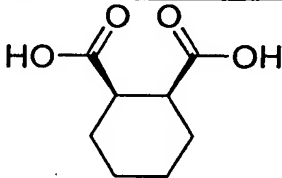
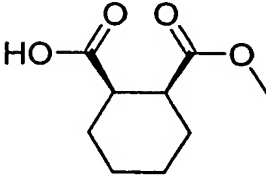
wherein R , A , R_3 , g , and n are as hereinbefore defined.

10 Many of the dicarboxylates or more advanced intermediates that are generically described in scheme IV are commercially available. Several of these are shown in Table 1. This table is used for illustrative purposes only and is not intended to limit the scope of the present invention in any way.

Starting Materials:

TABLE I

Structure	Name	CAS #	Supplier
	Dimethyl cis-1,2-cyclopropane dicarboxylate	826-34-6	Acros
	Dimethyl trans-1,2-cyclopropane dicarboxylate	826-35-7	Acros
	Dimethyl 1-methyl-trans-1,2-cyclopropane dicarboxylate	702-92-1	Acros
	Dimethyl 3-methyl-trans-1,2-cyclopropane dicarboxylate	28363-79-3	Acros
	trans-Cyclobutane-1,2-dicarboxylic acid dimethylester		Syntec
	trans-D, L-1,2-Cyclopentane-dicarboxylic acid	1461-97-8	Aldrich
	trans-2-Carbomethoxy cyclopentane-1-carboxylic acid		Rieke
	trans-1,2-Cyclohexane dicarboxylic acid	2305-32-0	Aldrich Acros
	trans-2-Carbomethoxy cyclohexane-1-carboxylic acid		Rieke

Structure	Name	CAS #	Supplier
	cis-1,2-Cyclohexane dicarboxylic acid	610-09-3	Acros
	cis-2-Carbomethoxy cyclohexane-1-carboxylic acid		Rieke

When not commercially available, the appropriate starting material may be obtained via standard synthetic methods.

5

When a compound of formula (I) is obtained as a mixture of enantiomers these may be separated by conventional methods such as crystallization in the presence of a resolving agent, or chromatography, for example using a chiral HPLC column.

- 10 Compounds of formula (I) have been found to exhibit affinity for dopamine receptors, in particular D_3 receptors, and are expected to be useful in the treatment of disease states which require modulation of such receptors, such as psychotic conditions. Preferred compounds of the present invention are those which have higher affinity for dopamine D_3 than dopamine D_2 receptors.

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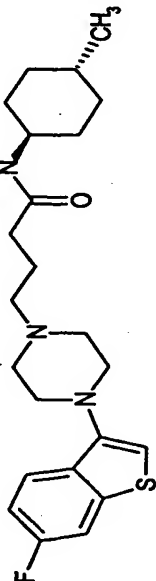
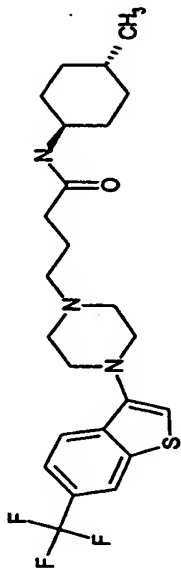
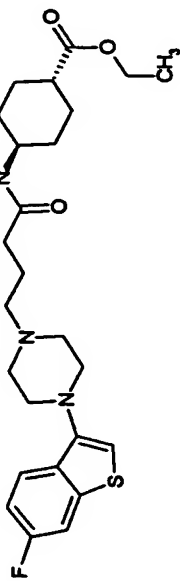
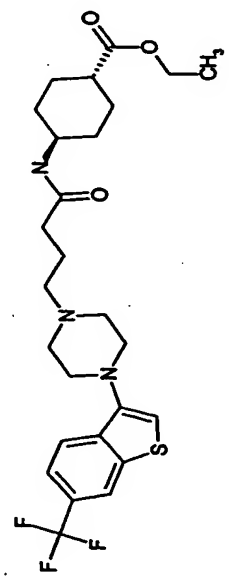
A major challenge in antipsychotic research is to produce agents with reduced side effects. Orthostatic hypotension is a common side effect in antipsychotics that is associated with the high potency that these agents have at the α -1 receptor (hereinafter referred to as " α -1"). A major goal of this work was to find agents with reduced α -1 potency.

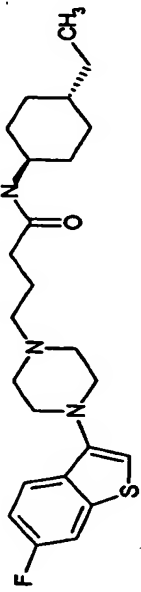
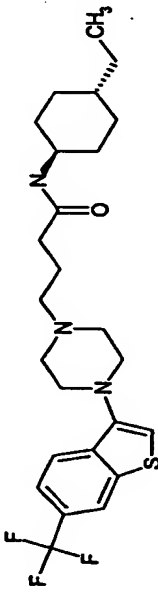
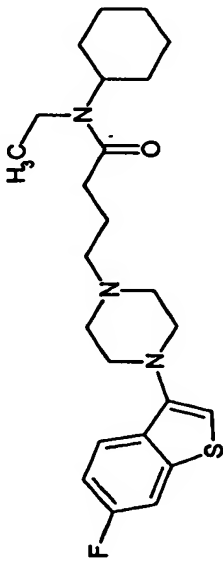
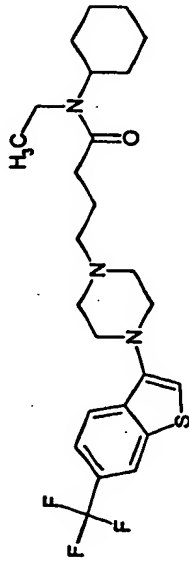
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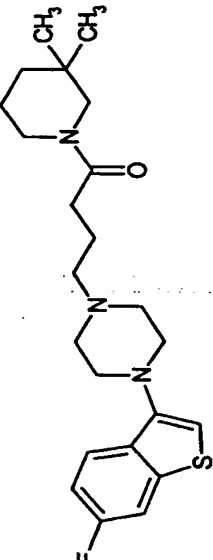
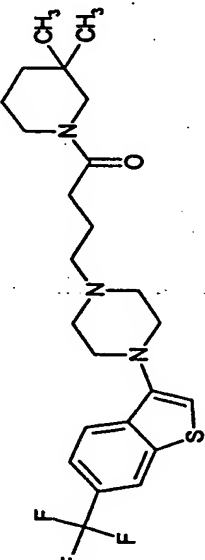
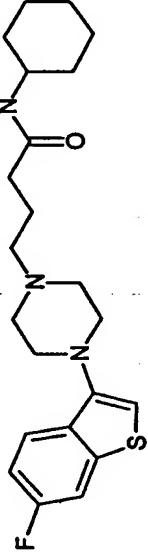
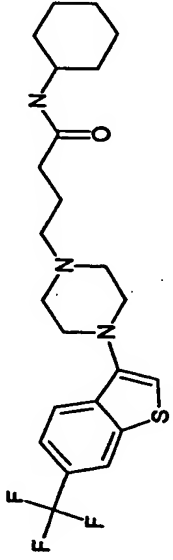
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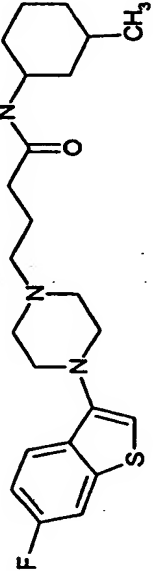
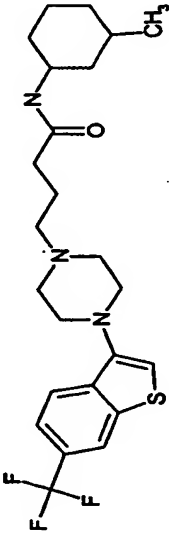
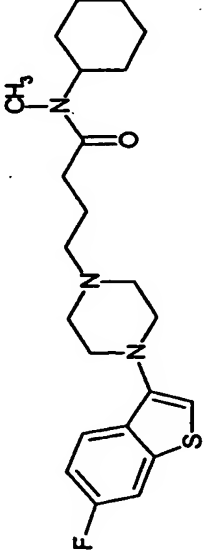
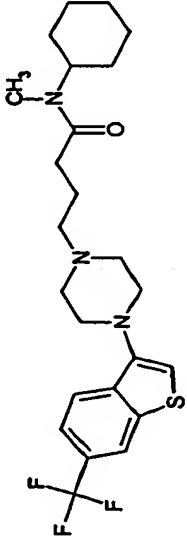
The 6-trifluoromethyl benzo[b]thiophenes described herein have a clear and somewhat surprising advantage over the 6-fluoro benzo[b]thiophenes as is shown in the following table. The 6-fluoro benzo[b]thiophenes are clearly more potent at the α -1 receptor than are the 6-trifluoromethyl benzo[b]thiophenes. This is shown by comparing pairs of analogs that only differ in substitution at the 6-position of the benzo[b]thiophene. In every case, the 6-fluoro benzo[b]thiophene is more potent than the corresponding 6-trifluoromethyl analog. In some cases this small structural difference in substitution at the 6-position produces a dramatic

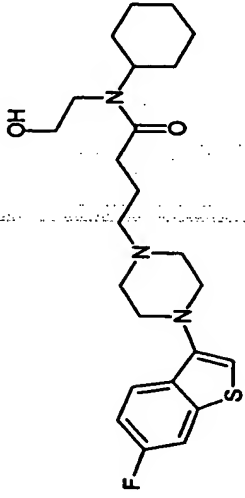
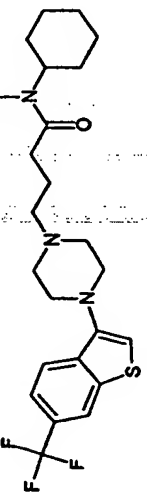
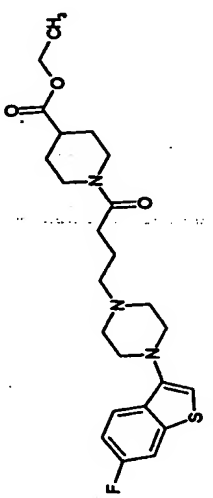
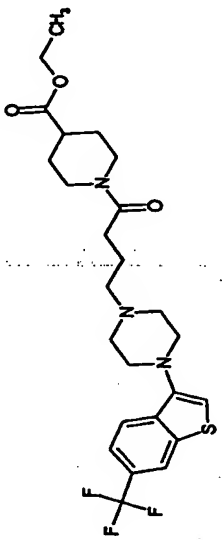
change in α -1 potency. There are several examples wherein 6-fluoro analogs exhibited nanomolar potency while the corresponding 6-trifluoromethyl analog exhibited micromolar potency.

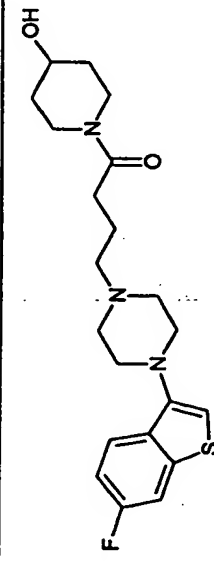

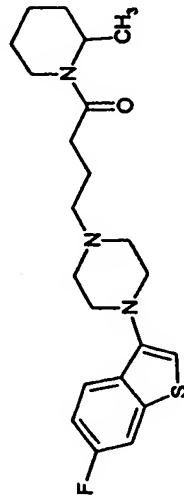
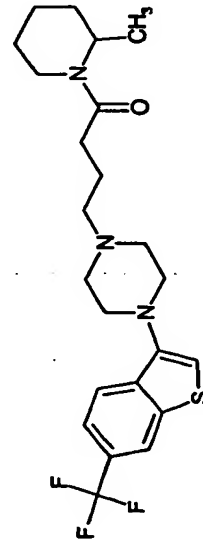
NUM	MOLSTRUCTURE	halpha1Ki (nM) h=human	halpha1 % I h=human
826844		23.4	
826804			32.8% Inh @ 1 uM
826845		5.44	
826805			27.8% Inh @ 1 uM

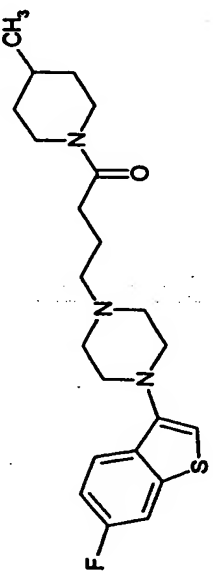
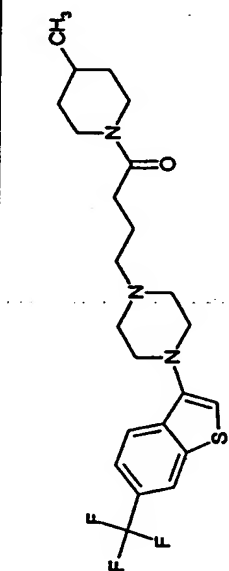
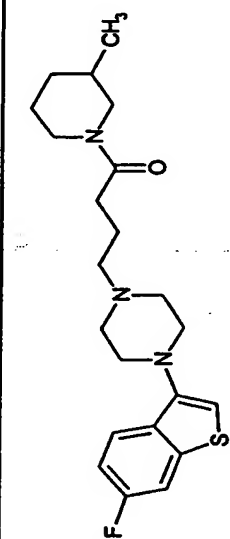
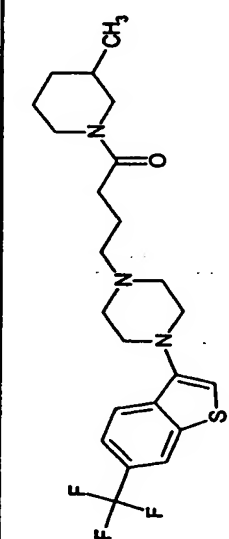
826846		93.9	
826806			10.3% Inh @ 1 uM
826849		35.2	
826809			30.5% Inh @ 1 uM


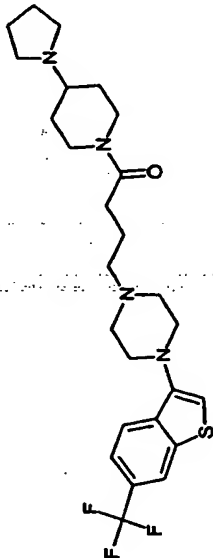
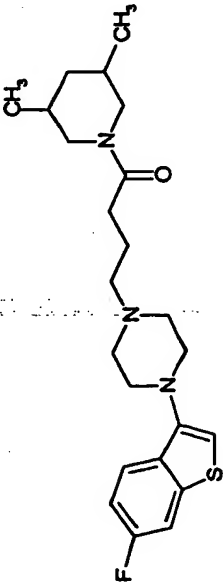
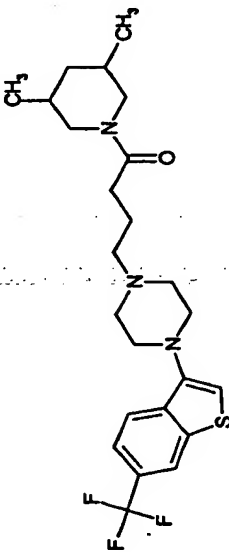
826857		9.82	
826817			44.4% Inh @ 1 uM
826861		9.55	
826821		1280	24% Inh @ 0.1 nM

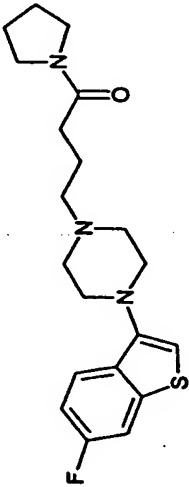
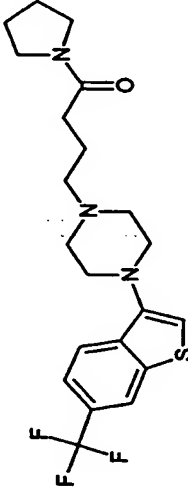
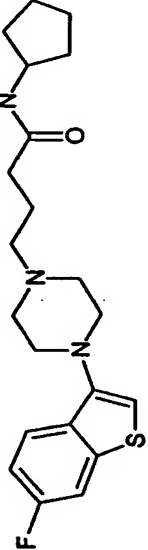
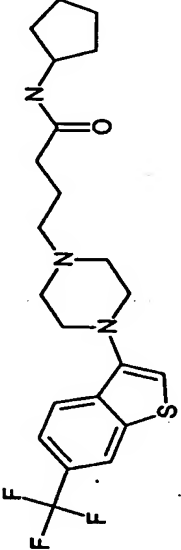
826847		0.513	
826807		166000	
826848		12.3	
826808		126	

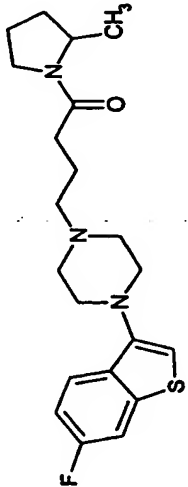
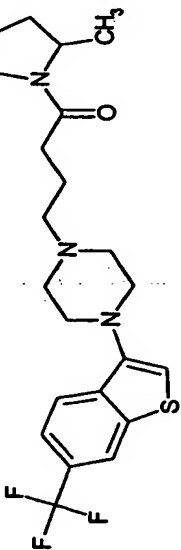
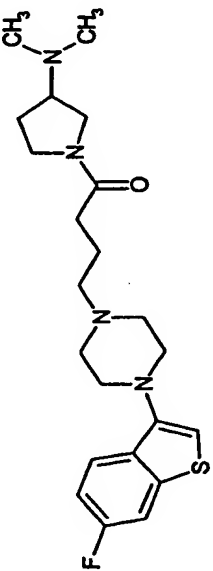
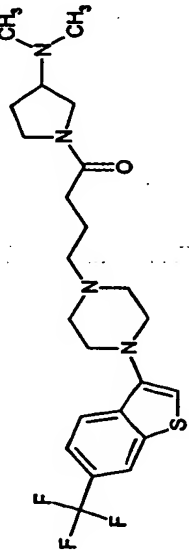
826850	 <chem>OCCC(=O)N(C1CCN(C1)c2cc(F)cc3sc23)CCN4CCCCC4</chem>	28.4	
826810	 <chem>OCCC(=O)N(C1CCN(C1)c2cc(C(F)F)cc3sc23)CCN4CCCCC4</chem>	200	
826851	 <chem>CCOC(=O)C1CCN(C1)C(=O)CCN2CCN(C2)c3cc(F)cc4sc34</chem>	18.9	
826811	 <chem>CCOC(=O)C1CCN(C1)C(=O)CCN2CCN(C2)c3cc(C(F)F)cc4sc34</chem>	223	

826852	 <chem>Oc1ccn(CCCC(=O)N2CCCN(C2)c3cc4cc(F)cc(s4)c3)c1</chem>	6.16	
826812	 <chem>Oc1ccn(CCCC(=O)N2CCCN(C2)c3cc4cc(C(F)F)cc(s4)c3)c1</chem>	658	
826853	 <chem>CN1CCCCC1C(=O)CCCN2CCCN(C2)c3cc4cc(F)cc(s4)c3</chem>	0.258	
826813	 <chem>CN1CCCCC1C(=O)CCCN2CCCN(C2)c3cc4cc(C(F)F)cc(s4)c3</chem>	57	

826854	 <chem>CC1CCN(C1)C(=O)CCN2CCN(C2)c3cc(F)ccc3</chem>	0.0713	
826814	 <chem>CC1CCN(C1)C(=O)CCN2CCN(C2)c3ccc(C(F)F)cc3</chem>	89.3	
826855	 <chem>CC1CCN(C1)C(=O)CCN2CCN(C2)c3cc(F)ccc3</chem>	0.889	
826815	 <chem>CC1CCN(C1)C(=O)CCN2CCN(C2)c3ccc(C(F)F)cc3</chem>	80.5	

826856		15.3	
826816		249	
826858		9.42	
826818		124	

826859	 <chem>O=C(CCCN1CCN(C1)c2csc3ccc(F)cc32)N4CCCC4</chem>	4	
826819	 <chem>O=C(CCCN1CCN(C1)c2csc3ccc(C(F)(F)c4ccccc43)cc2)N4CCCC4</chem>	49	
826860	 <chem>O=C(CCCN1CCN(C1)c2csc3ccc(F)cc32)N4CCCC4</chem>	0.516	
826820	 <chem>O=C(CCCN1CCN(C1)c2csc3ccc(C(F)(F)c4ccccc43)cc2)N4CCCC4</chem>	129	

826862	 <chem>CN1CCCC1C(=O)CCN2CCN(C2)c3sc4cc(F)ccc4c3</chem>	0.637	
826822	 <chem>CN1CCCC1C(=O)CCN2CCN(C2)c3sc4cc(C(F)(F)F)ccc4c3</chem>	32.2	
826863	 <chem>CN(C)C1CCN(C1)C(=O)CCN2CCN(C2)c3sc4cc(F)ccc4c3</chem>	32.2	
826823	 <chem>CN(C)C1CCN(C1)C(=O)CCN2CCN(C2)c3sc4cc(C(F)(F)F)ccc4c3</chem>	148	

Especially preferred compounds of the instant invention are those with a reduced liability for α -1 receptor binding while at the same time having a higher affinity for dopamine D₃ than dopamine D₂ receptors.

- 5 Receptor affinity can be measured using standard methodology such as is described below.

[N-Methyl-³H]Spiroperidol Binding to Cloned Human Dopamine D₃ Receptors

Purpose

10

This assay measures the *in vitro* activity of compounds on cloned human dopamine (D₃) receptors and predicts the direct dopamine-blocking properties of putative neuropsychiatric agents at human dopamine D₃ receptors.

Methods

15

A. Cloning

The D₃ gene was isolated from a human striatal cDNA library (Stratagene). The gene
20 was sequenced and sub-cloned into the expression vector RC/RSV (Invitrogen). CHO
(Chinese Hamster Ovary) cells were stably transfected with 10 μ g of the D₃/RSV plasmid
using the DOTAP method from Boehringer Mannheim and 72 clones that were G418
resistant were isolated. Using mRNA and binding displacement data a single high expressing
clone was identified. This clone was then grown in large batches for the purpose of
25 developing a 96 well format assay.

B. Cell Culture

1. One plate (10 cm) with approximately 2-3 million D₃ cells per plate is incubated with 1
30 ml of Trypsin-EDTA at room temperature for ~2 min or until cells have lifted off plates. Four
ml of Ham's F12 + 10% Fetal Bovine Serum + 1% Penicillin/Streptomycin + G418 (400
 μ g/ml) medium are added to resuspend cells and 1 ml of this is added to each large plate (15
cm) containing 19 ml of the same medium as mentioned above.

35 2. The 5 large plates are incubated at 37°C + 5% CO₂ for ~ 3 days or until the cells are
confluent.

3. After these plates are confluent, they are split into 10 large plates. Medium is aspirated off, 2 ml of Trypsin-EDTA are added to each plate and plates are incubated at RT for 2 min or until cells have lifted off the plate. Eight ml of the F12 medium (same medium as #1 above) are added to each plate (10 ml total) to resuspend the cells and 5 ml are transferred to the 2 new plates containing 15 ml of the F12 media.

4. The 10 large plates are incubated at 37°C + 5% CO₂ for ~ 2 days or until the cells are confluent.

5. The 10 large plates are split into 60 large plates (using Trypsin-EDTA as #3 except 4 ml of F12 medium are added to resuspend cells and 1 ml is aliquoted to 6 new plates containing 19 ml of F12 medium each).

6. Plates are incubated at 37°C + 5% CO₂ for ~ 3 days or until cell are confluent.

7. The 60 large plates are then split into 60 roller bottles (100-150 million cells/bottle). Medium is aspirated off, 2 ml of Trypsin-EDTA are added to each plate and incubated at RT for ~2 minutes or until cells have lifted off plates. Eight ml of F12 medium are added to each plate to resuspend cells and the entire 10 ml are added to 1 roller bottle containing 90 ml of the F12 medium.

8. The 60 roller bottles are immediately placed on their sides and transferred to the roller bottle incubator. They are incubated at 37°C + 5% CO₂ for ~ 3-5 days. Cells are spun at 30-40% motor speed in the Forma incubator.

9. Medium is poured off and cells are washed 2X in PBS.

10. Cells are then scraped off in 20 ml of PBS and the bottles are rinsed again with 5 ml of PBS to remove any remaining cells. Cells are stored on ice before membrane preparation.

11. The yield for 60 D₃ roller bottles has varied from ~ 260-500 mg.

Note: All tissue culture reagents are from Gibco-BRL.

C. Membrane Preparation

The cells are harvested into 250 ml centrifuge tubes with 100 volumes of cold phosphate buffered saline (PBS) and spun down (1200xG for 10 min at 4°C). The medium is removed and 100 ml PBS are added to each centrifuge tube, cells are resuspended and spun down again. The PBS is removed and the final pellet is homogenized in an appropriate volume of 10% DMSO with a polytron on ice at a medium setting.

D. Lowry Protein Assay

A 200 µl sample membrane homogenate is added to 200 µl of 1% SDS, vortexed and allowed to stand for 5 min. Aliquots (25, 50 and 100 µl) of this mixture are assayed in duplicate following the standard Bio-Rad DC protein assay protocol (kit catalog number 500-0112) and using reagent S. Absorbance readings are made at 750 nm (note: the most accurate protein OD readings are between 0.1-0.5 units). The protein concentration is calculated using a standard curve generated concurrently with bovine serum albumin as standard.

E. Storage/Freezing conditions

Following the determination of the protein concentration and Scatchard analysis, the protein is diluted into distilled water with 10% DMSO to the appropriate volume based on expression levels (B_{max}). The concentrated protein is then aliquoted into 1.5 ml screw top cap Eppendorf tubes and placed into a -80°C freezer.

F. Binding Assay Reagents

1. 0.5M Tris Buffer, pH 7.7

- a) 44.4 g Tris HCl
- 26.5 g Tris Base
- q.s. to 1 Liter (0.5 M Tris buffer, pH 7.7 at 37°C)

- b) make a 1:10 dilution in distilled H₂O (0.05 M. Tris buffer, pH 7.7)

2. Tris Buffer containing physiological salts

a) Stock buffer

NaCl 7.014 g

KCl 0.372 g

CaCl₂ 0.222 gMgCl₂ 0.204 g

q.s. To 100 ml with 0.5 M. Tris Buffer

b) Dilute 1:10 in distilled H₂O

10 This yields 0.05 M. Tris HCl, pH 7.7, containing NaCl (120 mM), KCl (5 mM), CaCl₂ (2 mM) and MgCl₂ (1 mM)

Optional: add 0.1% ascorbic acid and check pH (in assays with compounds that may oxidize).

15 3. a) 1.0 % polyethyleneimine stock in 0.5M Tris (reagent 1.a)

b) Dilute 1:10 in distilled H₂O

4. [N-methyl-³H]-Spiroperidol (60-90 Ci/mmol) is obtained from New England Nuclear; catalog #NET-856.

20 For K_i determinations: [³H]NMSP is made up to a concentration of 2.7 nM in buffer 2b, such that when 150 µl is added to each tube a final concentration of 0.4 nM is attained in the 1 ml assay. Samples of total CPM added are taken for each experiment to calculate the total ligand concentration.

25 5. S(-)-Eticlopride is obtained from Research Biochemicals International (RBI catalog number E-101). A refrigerated stock (good for up to a month) solution of S(-)-eticlopride is made at a concentration of 30 µM in buffer 2b. One hundred microliters are added to 3 wells for the determination of nonspecific binding (this yields a final concentration of 30 3 µM in the 1 ml assay).

6. Test Compounds

For most assays, a 100 µM stock solution of the test compound is made up in a suitable solvent (usually <0.1% acetic acid) and serially diluted with buffer 2b, such that when 100 µl of 35

drug is combined with the total 1 ml assay, final concentrations ranging from 10^{-5} - 10^{-8} M are attained. Characteristically eight concentrations are studied for each assay; however, higher or lower concentrations may be used, depending on the potency of the drug.

5 G. Binding Assay

750 μ l Tissue

150 μ l [3 H]NMSP

100 μ l vehicle (for total binding) or 30 μ M (-)eticlopride (for nonspecific
10 binding) or appropriate drug concentration.

The 96-Well Packard Unifilters GF/B are incubated for >1 h at 25°C in 0.1% polyethylamine (from 3,b). The cold tissue is added last and mixed on a orbital shaker for a few seconds and is then incubated at 37°C for 30 min in a shaking water bath. The assay is
15 stopped by rapid filtration through Packard Unifilter plates. The filter membranes are then washed with 15 ml of ice-cold 0.05 M Tris buffer. The filters are then dried (~15 min under a heat lamp or incubated for 15 min in a 60°C oven) and a bottom seal is applied. Then 40 μ l of Packard Microscint 20 scintillation cocktail is added and a permanent topseal (Type P) is applied and heat sealed. The plates are then shaken on an orbital shaker for 1 h and placed in
20 the Packard Topcount and counted for at least 5 minutes for each point.

Specific binding is defined as the difference between total binding and the binding in the presence of 3 μ M S(-)-eticlopride. Total binding is approximately 10% of the total added ligand. Cheng -Prusoff determination (K_i 's) are performed using Prism software using a one-
25 site competition curve analysis where the top and the bottom of the non-linear regression are held constant at 0% and 100% percent inhibition. The percent inhibition at each drug concentration is the mean of duplicate determinations.

30 **[N-Methyl- 3 H]Spiroperidol Binding to Cloned Human Dopamine D₂Long Receptors**

Purpose:

This assay measures the *in vitro* activity of drugs on cloned human dopamine D₂Long (D₂L) receptors and predicts the direct dopamine-displacing properties of neuropsychiatric,
35 cardiovascular and renal agents at human dopamine D₂ receptors.

Methods:**A. Cloning**

5 The D₂L gene was isolated from a human striatal (caudate/putamen) cDNA library. The gene was sequenced and sub-cloned into the expression vector pRC/RSV (Invitrogen). CHO (Chinese Hamster Ovary) cells were stably transfected and 72 clones that were geneticin (G418) resistant were isolated. Using mRNA and binding data a single high expressing cell line was identified (#44). This cell line was then grown in suspension culture
10 for the purpose of developing a 96 well format assay.

B. Cell Culture Conditions**1. Medium for adherent CHO cultures:**

15 Ham's F12 + 10% fetal bovine serum (FBS) + 400 µg/ml geneticin
 (G418) + 10 ml/L penicillin-streptomycin (pen-strep)

2. Cells are transferred to suspension culture when at least 1.5 million cells are available (this allows for 300,000 cells/ml in a 50 ml spinner flask; this is the ideal suspension density).

20 Cell are removed from flasks with trypsin, spun down (1000xG) and resuspended in fresh medium:

 50% CHO-SFM II + 50% Ham's F12 w/ 10% FBS (final FBS conc. 5%)
 + 400 µg/ml G418 + pen-strep (10 ml/L)

25 3. After the transfer to suspension culture, growth is monitored and cell viability is assessed using trypan blue exclusion. Total and viable cell count on 5 sectors of the hemocytometer are recorded. When the viable cell density reaches 600,000 cell/ml, the volume is doubled.

30 4. After 1 week of growth in the 50/50 medium, the cells are spun down and transferred to a new spinner flask and replaced with 75% CHO-SFM II / 25% Ham's F12 + 10% FBS plus the pen-strep and G418. Thereafter every 3 days, the medium is replaced with new medium containing a decreasing amount of FBS as follows:

	ml of CHO SFM:	ml of Ham'S F12	Final % FBS conc.
35		87.50 : 12.5	1.25
		93.75 : 6.25	0.625
		99.00 : 1.00	0.1

5. The final maintenance culturing medium is made up as follows:

A stock mixture of 10 ml of pen-strep, 0.5 ml of 400 mg/ml (active; final concentration: 200 mg/ml) G418 and 1ml of FBS are mixed and filtered and refrigerated. A volume (11.5 ml) of this mixture is added to a freshly opened 1-L bottle of CHO-SFM II.

C. Membrane Preparation

The cells are harvested into 250 ml centrifuge tubes with 100 volumes of cold phosphate buffered saline (PBS) and spun down (1200xG for 10 min at 4°C). The medium is removed and 100 ml PBS are added to each centrifuge tube, cells are resuspended and spun down again. The PBS is removed and the final pellet is homogenized in an appropriate volume of PBS with a polytron on ice at a medium setting.

D. Lowry Protein Assay

A 200 µl sample membrane homogenate is added to 200 µl of 1% SDS, vortexed and allowed to stand for 5 min. Aliquots (25, 50 and 100 µl) of this mixture are assayed in duplicate following the standard Bio-Rad DC protein assay protocol (kit catalog number 500-0112) and using reagent S. Absorbance readings are made at 750 nm (note: the most accurate protein OD readings are between 0.1-0.5 units). The protein concentration is calculated using a standard curve generated concurrently with bovine serum albumin as standard.

E. Storage/Freezing conditions

Following the determination of the protein concentration, the protein is diluted into distilled water with 10% DMSO to the appropriate volume based on expression levels (Bmax). The concentrated protein is aliquoted into 1.5 ml screw top eppendorf tubes and placed into a -80°C freezer.

F. Binding Assay Reagents

1. 0.5M Tris Buffer, pH 7.7

a) 44.4 g Tris HCl

26.5 g Tris Base

q.s. to 1 Liter (0.5 M Tris buffer, pH 7.7 at 37°C)

b) make a 1:10 dilution in distilled H₂O (0.05 M. Tris buffer, pH 7.7)

5

2. Tris Buffer containing physiological salts

a) Stock buffer

NaCl 7.014 g

KCl 0.372 g

CaCl₂ 0.222 g

MgCl₂ 0.204 g

q.s. To 100 ml with 0.5 M. Tris Buffer

10

b) Dilute 1:10 in distilled H₂O

15

This yields 0.05 M. Tris HCl, pH 7.7, containing NaCl (120 mM), KCl (5 mM), CaCl₂ (2 mM) and MgCl₂ (1 mM)

Optional: add 0.1% ascorbic acid and check pH (in assays with compounds that may oxidize).

20 3. a) 1.0 % polyethyleneimine stock in 0.5M Tris (reagent 1.a)

b) Dilute 1:10 in distilled H₂O

4. [N-methyl-³H]-Spiroperidol (60-90 Ci/mmol) is obtained from New England Nuclear; catalog #NET-856.

25

For K_i determinations: [³H]NMSP is made up to a concentration of 2.7 nM in buffer 2b, such that when 150 µl is added to each tube a final concentration of 0.4 nM is attained in the 1 ml assay. Samples of total CPM added are taken for each experiment to calculate the total ligand concentration.

30

5. S(-)-Eticlopride is obtained from Research Biochemicals International (RBI catalog number E-101). A refrigerated stock (good for up to a month) solution of S(-)-eticlopride is made at a concentration of 30 µM in buffer 2b. One hundred microliters are added to 3 wells for the determination of nonspecific binding (this yields a final concentration of 3 µM in the 1 ml assay).

35

6. Test Compounds

For most assays, a 100 μ M stock solution of the test compound is made up in a suitable solvent (usually <0.1% acetic acid) and serially diluted with buffer 2b, such that when 100 μ l of drug is combined with the total 1 ml assay, final concentrations ranging from 10^{-5} - 10^{-8} M are attained. Characteristically eight concentrations are studied for each assay; however, higher or lower concentrations may be used, depending on the potency of the drug.

G. Binding Assay

750 μ l Tissue

150 μ l [3 H]NMSP

100 μ l vehicle (for total binding) or 30 μ M (-)eticlopride (for nonspecific binding) or appropriate drug concentration.

The 96-Well Packard Unifilters GF/B are incubated for >1 h at 25°C in 0.1% polyethylamine (from 3,b). The cold tissue is added last and mixed on a orbital shaker for a few seconds and is then incubated at 37°C for 30 min in a shaking water bath. The assay is stopped by rapid filtration through Packard Unifilter plates. The filter membranes are then washed with 15 ml of ice-cold 0.05 M Tris buffer. The filters are then dried (~15 min under a heat lamp or incubated for 15 min in a 60°C oven) and a bottom seal is applied. Then 40 μ l of Packard Microscint 20 scintillation cocktail is added and a permanent topseal (Type P) is applied and heat sealed. The plates are then shaken on an orbital shaker for 1 h and placed in the Packard Topcount and counted for at least 5 minutes for each point.

Specific binding is defined as the difference between total binding and the binding in the presence of 3 μ M S-(-)-eticlopride. Total binding is approximately 10% of the total added ligand. Cheng -Prusoff determination (K_i 's) are performed using Prism software using a one-site competition curve analysis where the top and the bottom of the non-linear regression are held constant at 0% and 100% percent inhibition. The percent inhibition at each drug concentration is the mean of duplicate determinations.

**³H]PRAZOSIN BINDING TO CLONED HUMAN ALPHA-1A ADRENERGIC RECEPTORS (α_{1a})
EXPRESSED IN CHINESE HAMSTER OVARY CELLS (CHO)**

Purpose:

This *in vitro* assay is designed as a screen to identify compounds displaying a affinity for the human α_{1a} adrenoceptor subtype expressed in the membrane fragments of CHO cells. The assay measures the ability of the test compounds to displace [³H] prazosin from α_{1a} sites.

The identification of multiple vascular α_1 -adrenoceptors (α_{1a} , α_{1b} , α_{1d}) *in vitro* has provided impetus to define the role(s) of these subtypes in cardiovascular regulation *in vivo* (Vargas and Gorman, 1995). Hemodynamic studies in the unanesthetized rat suggest that vascular α_{1a} receptors are the major subtype involved in the sympathetic regulation of peripheral resistance and systemic arterial pressure (Piascik et al., 1989). Additional evidence for an involvement of peripheral α_{1a} receptors in the maintenance of arterial pressure was demonstrated by the findings that the selective α_{1a} antagonist 5-MU dose dependently lowered resting arterial pressure in awake conscious dogs (Piascik et al., 1989). A demonstrated inability of the irreversible antagonist, chloroethylclonidine, to reduce arterial pressure in rats when administered intravenously, is strong evidence against the role of α_{1b} and α_{1d} receptors in the acute regulation of arterial pressure (Vargas et al., 1993).

Therefore, the binding of compounds to α_{1a} adrenergic receptors is believed to be a good measure of a compound's potential to cause orthostatic hypotension and sedation as side effects. Prazosin is a potent antagonist of the human α_{1a} -adrenoceptor subtype, which has been cloned and is expressed in the membrane fragments of CHO cells.

h α_{1a} receptor:

The cloning of the human α_{1a} cDNA was accomplished first by screening a human prostate cDNA library (Clontech), from which a portion of the coding region was obtained. This DNA fragment was then used to screen a human leukocyte genomic library (Clontech), and the rest of the coding sequence was obtained. Later these two

fragments were spliced together. The entire coding sequence was then fully sequenced including matching PCR sequence with original genomic coding sequence, thus ensuring splice sites were joined correctly (Schwinn et al., 1995). Once sequenced, the gene was subcloned into the expression vector pcDNA3 (Invitrogen). Plasmid DNA was then used for transfection into CHO cells and G418 resistant clones were isolated. A clone expressing high levels of the α_{1a} receptor (as determined by mRNA and receptor binding data) was chosen and pharmacologically characterized.

Culture Media:

Media Ingredients for Adherent α_{1a} expressing CHO Culture:

- A. HAM's F-12 (Cellgro)
- B. 10% 0.2 micron filtered Fetal Bovine Serum (FBS)(Cellgro)
- C. 1% 0.2 micron filtered Penicillin-Streptomycin (Cellgro)
- D. G418 0.2 micron filtered (Geneticin 400 μ g/ml)(Cellgro)

Cells are cultured using established methods and procedures in either 150x25mm culture plates (scale up to 100 plates) or a combination of these plates and 70 roller bottles. One culturing/harvest cycle typically requires 2 weeks and yields between 100-400mg protein. Plates or bottles are incubated at 37°C + 5% CO₂.

Storage:

Cells are harvested by mechanical scraping, washed using PBS, collected in 250ml Corning polypropylene centrifuge tubes, spun down (1500RPM) and resuspended in dH₂O 10% DMSO (final volume per harvest is approximately 50ml). Protein determination is made using the Biorad DC Assay Kit. Finally, the appropriate volume is aliquoted into a 2ml Corning Cryovial (10mg/1-1.5 ml) which is stored at -80°C.

Current Lot Data:

α_{1a} (clone # 7)

Batch 1/14/98

Receptor Concentration 2418 fmoles/mg protein

K_d 0.18nM

Volume 1.5 ml/cryovial

Protein Concentration approx. 10mg/1.5ml

Assay Requirement: 0.5 cryovials per 96 well plate (assay volume = 200 μ l/well)

[³H]-Ligand: [7-methoxy-³H]-Prazosin: 1.0nM (NEN, NET-823)
70-87 Ci/mmol

Materials: Phentolamine mesylate (Research Biochemicals Int. #P-131)
96 well flat bottom plates (Beckman)
Unifilter GF/B Plate (Packard)
Polyethylenimine (Sigma #P-3134)
TomTec or Packard Filtermate 196 Cell Harvesters
Packard TopCount Scintillation Counter

Buffers: **A:** 50 mM Tris-HCl; 0.1% ascorbate, pH 7.7 (incubation buffer)
B: 50 mM Tris HCl; pH 7.7 (wash buffer)

Procedure: Assay additions are as follows (in the order indicated):
Total Binding = 50μl buffer A + 50μl [³H]prazosin + 100μl membrane
Nonsp. Bd. = 50μl 10μM phentolamine+50 μl [³H]prazosin+100μl membrane
Test Cpd. = 50μl compound + 50μl [³H]prazosin + 100μl membrane

Compounds to be evaluated are weighed out to yield a 10 mM stock solution in DMSO in a 24 well polystyrene plate. This is diluted to a 0.5 mM stock in dH₂O. Serial dilutions in Buffer A are made from which 50 μl additions to the plate are made in duplicate in order to achieve the final concentrations desired. Typically, one 96 well plate is used to evaluate 11 compounds at 4 concentrations (10⁻⁶-10⁻⁹ M) in duplicate. Total binding and nonspecific binding are determined in quadruplicate. Usually one standard is run with each assay.

[³H]Prazosin is made up in Buffer A such that when 50 μl are added per well the final concentration is 1.0 nM in a final assay volume of 200 μl. The final concentration should be verified by running a sample in a scintillation counter prior to adding the [³H]prazosin to the 96 well plate. Note: The radioactivity should be prepared just before the additions are made so that it is not allowed to sit on the bench for very long.

Packard GF/B Plate Pretreatment: The filter plates are presoaked for at least 30 min in ice cold Buffer B containing 0.05% polyethyleneimine

(200 μ l/200 ml) to maximize filtration efficiency and minimize filter blank binding.

Incubation & Filtration: Once buffer, compounds, [3 H]prazosin and membrane have been added (and mixed), the 96 well plates are incubated for 40 min at 37°C and spaced 3-5 min apart. At 40 min, the plates are filtered using a Tomtec Automated Cell Harvester. Filtration is immediately followed by washes of ice cold Buffer B (total vol. ~7 ml).

Drying and Counting: Each filter plate is dried under a heat lamp for 15 min. The back of the plate is sealed and 40 μ l of Packard microscint fluid are added per well. Using Packard film, each plate is heat sealed prior to being counted in a Packard Topcount Scintillation counter. A program has been written that counts each plate twice sending DPM, CPM and TSIS data to disk and printer.

Analysis of Results: Raw DPM and CPM data are captured on disk and are imported into one of several software packages (Graphpad Prism Ver 2.0, Excel) residing on the LAN. Specific binding is defined as the difference between total binding and the binding in the presence of 10 μ M phentolamine. Total binding is less than 10% of the total added ligand. Software using one-site competition curve analysis is employed in the calculation of IC_{50} and K_i (Cheng-Prusoff equation, 1973). The top and bottom of the non-linear regression are held constant at 0% and 100% inhibition. The percent inhibition at each drug concentration is the mean of duplicate determinations.

References:

- Vargas, H.M and A.J. Gorman. *Life Sciences*. Vol. 57, No. 25, pp. 2291-2308, 1995.
- Morrow, A.L. and I. Creese. *Mol. Pharmacol.* 29: 321-330, 1986.
- Piasek, M.T., J.W. Kusiak, and K.W. Barron. *Eur. J. Pharmacol.* 11:101-107, 1989.
- Vargas, H.M., D. Cunningham, L. Zhou, H.B. Hartman and A.J. Gorman. *J. Pharmacol. Exp. Ther.* 267:264-272, 1993.

5 The functional activity of compounds of the invention (i.e. whether they are antagonists, agonists or partial agonists) can readily be determined using the microphysiometer test method that follows:

10 Chinese Hamster Ovary (CHO) cells, expressing the human dopamine D₃ receptor, were grown on the surface of a capsule cup. Cups are assembled and placed on the microphysiometer, and buffer (Dulbecco's Modified Eagle's Medium without sodium bicarbonate and without serum) is perfused through the cup assembly until a stable baseline is achieved (4 hours). Buffer perfusion rate and solution changes are controlled by a computer. Intracellular acidification rate is measured in each of the 8 cup assemblies and
15 recorded by the computer. Buffer containing test compound (10 nM, 100 nM, and 1 uM) was perfused through the cup assembly for 20 min, then buffer containing quinpirole (a D₃ agonist) (10 nM) and test compound (same concentrations) is perfused for an additional 1 min. This is followed by a recovery period of 10-60 min where buffer alone is perfused through the cups. Quinpirole increases acidification rate. A D₃ antagonist will inhibit this acidification rate in a
20 concentration dependent manner.

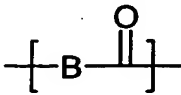
 D₃ antagonists are of potential use as antipsychotic agents for example in the treatment of schizophrenia, schizo-affective disorders, psychotic depression and mania. Conditions which may be treated by D₃ agonists include include dyskinetic disorders such as
25 Parkinson's disease, neuroleptic-induced parkinsonism and tardive dyskinesias; depression; anxiety; dementia; circadian rhythm disorders, and drug (e.g. cocaine) dependency.

 In accordance with yet another embodiment of the present invention, there is provided a method of modulating the activity of dopamine D₃ receptors, said method comprising:
30 contacting cell-associated dopamine D₃ receptors with a concentration of a compound of formula IB, or a physiologically acceptable salt thereof, sufficient to modulate the activity of said dopamine D₃ receptor. As employed herein, a compound of formula IB shall refer to the compound of formula I except that the proviso therein is deleted therefrom.

35 As employed herein, the phrase "modulating the activity of dopamine D₃ receptors" refers to a variety of therapeutic applications. Said therapeutic applications refer to the treatment of conditions or disorders which include dyskinetic disorders, psychoses, anxiety

disorders, mood disorders, dementia, sleep disorders, nausea substance dependence, substance abuse and nausea.

The instant invention also provides a method of treating conditions or disorders of the central nervous system comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula I, IA, or IB or a pharmaceutically acceptable salt thereof. The compounds of formula IA are preferred for this method. As employed herein, a "compound of formula IA" shall refer to the compound of formula I except that the proviso therein i.e. "Proviso A" is deleted therefrom and inserted therefor is the following proviso (hereinafter referred to as "Proviso B"):

"when n is 2, R₃ is hydrogen or C₁-C₆alkyl,  is a group of formula (a), and R is group:

(a) wherein R₄ is hydrogen, halogen or C₁-C₆alkyl, and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

- (a) wherein z is 0,
- (b) wherein u is 0 and M is hydrogen, halogen, C₁-C₆alkyl, or trifluoromethyl,
- (c) wherein o is 0,
- (d) wherein l is 0,
- (e) wherein j is 0,
- (g) wherein v is 0, or
- (i);

and also when R is the group of formula (a), R₁ and R₂ cannot be joined together to form the group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl;

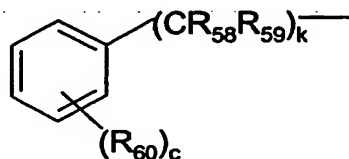
(b) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

- (a),
- (b),

- (d) wherein I is 0,
 (k),
 (l), or
 (m) wherein Q is CH₂;

and also when R is the group of formula (b), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or

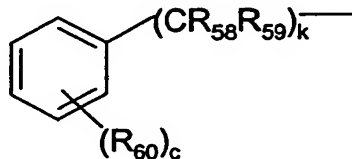


- (d) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

- (a),
 (b) wherein u is 1,
 (d),
 (k),
 (l), or
 (m) wherein Q is CH₂;

and also when R is the group of formula (d), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or



- (e) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

- (a),
 (b),

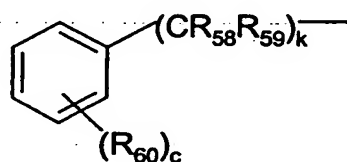
- (d),
 (k),
 (l), or
 (m) wherein Q is CH₂;

5

and also when R is the group of formula (e), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

10

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or



(f) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

15

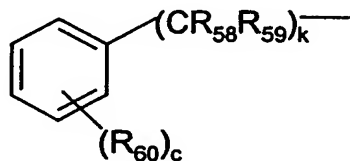
- (a),
 (b),
 (d),
 (k),
 (l), or
 (m) wherein Q is CH₂;

20

and also when R is the group of formula (f), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

25

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or



(g) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

30

- (a),
 (b) wherein u is 1,

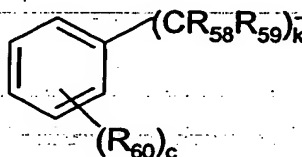
- (d),
 (k),
 (l), or
 (m) wherein Q is CH₂;

5

and also when R is the group of formula (g), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or

10



(h) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

15

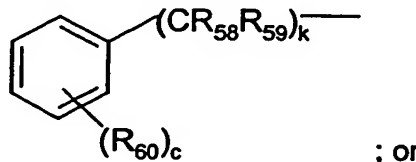
- (a),
 (b),
 (d),
 (k),
 (l), or
 (m) wherein Q is CH₂;

20

and also when R is the group of formula (h), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

25

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or



(j) then R₁ and R₂ cannot be joined together to form a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

30

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl".

The instant invention further provides a method of treating conditions or disorders of the central nervous system comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula I, IA or IB or a pharmaceutically acceptable salt thereof, in conjunction with one or more D₁, D₂, D₄, D₅ or 5HT receptor antagonists. Compounds of formula IA are preferred for this method.

In treating a patient afflicted with a condition or disorder described above, a compound of formula I, IA, or IB can be administered in any form or mode which makes the compound bioavailable in therapeutically effective amounts, including orally, sublingually, buccally, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, topically, and the like. One skilled in the art of preparing formulations can determine the proper form and mode of administration depending upon the particular characteristics of the compound selected for the condition or disease to be treated, the stage of the disease, the condition of the patient and other relevant circumstances. For example, see Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990), incorporated herein by reference.

The compounds of Formula I, IA, or IB can be administered alone or in the form of a pharmaceutical composition in combination with pharmaceutically acceptable carriers, the proportion and nature of which are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, standard pharmaceutical practice and other relevant criteria.

The compounds of formula I, IA, or IB may be administered orally, for example, in the form of tablets, troches, capsules, elixirs, suspensions, solutions, syrups, wafers, chewing gums and the like and may contain one or more of the following adjuvants: binders such as microcrystalline cellulose, gum tragacanth or gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings

and flavors.

The compounds of Formula I, IA, or IB may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment or gel base. The base, for example, may comprise one or more of petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers.

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials.

The highly lipophilic esters, amides and carbamates of compounds I, IA, or IB are capable of sustained release in mammals for a period of several days or from about one to four weeks when formulated and administered as depot preparations, as for example, when injected in a properly selected pharmaceutically acceptable oil. The preferred oils are of vegetable origin such as sesame oil, cottonseed oil, corn oil, coconut oil, soybean oil, olive oil and the like, or they are synthetic esters of fatty acids and polyfunctional alcohols such as glycerol or propyleneglycol.

The depot compositions of formula I, IA, or IB are prepared by dissolving a highly lipophilic ester, amide or carbamate of the instant invention in a pharmaceutically acceptable oil under sterile conditions. The oil is selected so as to obtain a release of the active ingredient over a desired period of time. The appropriate oil may easily be determined by consulting the prior art, or without undue experimentation by one skilled in the art.

The dosage range at which the compounds of formula I, IA, or IB exhibit their ability to act therapeutically can vary depending upon the particular disease or condition being treated and its severity, the patient, the formulation, other underlying disease states that the patient is suffering from, and other medications that may be concurrently administered to the patient.

Generally, the compounds of formula I, IA or IB will exhibit their therapeutic activities at dosages of between about 0.001 mg/kg of patient body weight/day to about 100 mg/kg of patient body weight/day.

In a further aspect, the present invention provides novel radiolabeled imaging agents of formula I, IA, or IB useful, inter alia, for imaging dopamine D₃ receptors in the CNS to diagnose CNS abnormalities.

5

In a further aspect, the present invention provides novel radiolabeled imaging agents of formula I, IA, or IB useful, inter alia, for imaging dopamine D₃ receptors in the CNS to diagnose CNS abnormalities.

10 The radiolabeled (tritiated and C-14 labeled) forms compounds of formula I, IA, or IB are useful as radioligands to determine the binding of compounds to the dopamine D₃ receptor. They are also useful as labeled parent compounds to determine the metabolism of the compound in animals. Preferred for this purpose are compounds of formula I and IA wherein R is group (a) with a radiolabeled ¹⁴C in the 3-position of the benzo[b]thiophene ring, 15 R₄ is trifluoromethyl, s is 1, R₃ is hydrogen, n is 2 and A is N. Particularly preferred for this purpose are compounds of formula IC. As employed herein, a "compound of formula IC" shall refer to the compound of formula I wherein R is group (a) with a radiolabeled ¹⁴C in the 3-position of the benzo[b]thiophene ring, R₄ is trifluoromethyl in the 6-position of the benzo[b]thiophene ring, s is 1, R₃ is hydrogen, n is 2 and A is N. Compounds of formula IC 20 may be prepared in a manner analogous to that set forth in Example 33.

Imbalances in dopamine production have been implicated in a variety of mental and physical disorders, such as Parkinson's disease (PD). It is thus desirable to diagnose and monitor such imbalances and to monitor the effectiveness of drugs and substances that affect 25 brain chemistry. New and powerful imaging methods that enable one to assess the living brain in vivo and thereby monitor brain chemistry and the effectiveness of drugs and substances that affect brain chemistry have been developed. Methods such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) involve administering to a patient a radioactive tracer substance comprising a ligand that binds 30 to the presynaptic or postsynaptic neuroreceptors in the patient's brain. Emissions (primarily gamma rays are emitted from the positrons or photons from the radioactive tracer) are measured. These emissions are indicative of the number and degree of occupancy of blocking of the neuroreceptors. The number of neuroreceptors and the degree of occupancy or blocking is calculated utilizing a mathematical model, and compared with an intra-person or 35 inter-person control to determine the degree of drug response. Further treatment of the patient with drugs is based on the comparisons made. For these methods to be useful, however, a ligand that has a high specificity and affinity for the desired receptor is required.

It is believed that certain radioactive ligands may be selective for dopamine transporters and are thus potentially useful in evaluating changes in dopamine function in vivo and in vitro, especially for patients with Parkinson's disease (PD), which is characterized by a selective loss of dopamine neurons in the basal ganglia and substantia nigra.

Another aspect of this invention relates to methods for utilizing the compounds of the invention as CNS imaging agents. Imaging techniques are non-invasive diagnostic techniques that generally involve administering a compound with marker atoms that can be detected externally to the mammal. Generally, these methods comprise administering to a mammal a compound of the invention, dissolved or dispersed in a suitable pharmaceutical carrier or diluent. The compound of the invention selectively binds to dopamine D₃, thus permitting the imaging of CNS receptors and the ability to, inter alia, evaluate brain chemistry, the effectiveness of drugs, and neuronal functions. Imaging techniques suitable for practicing the present invention include, but are not limited to, single photon emission computed tomography (SPECT) and positron emission tomography (PET).

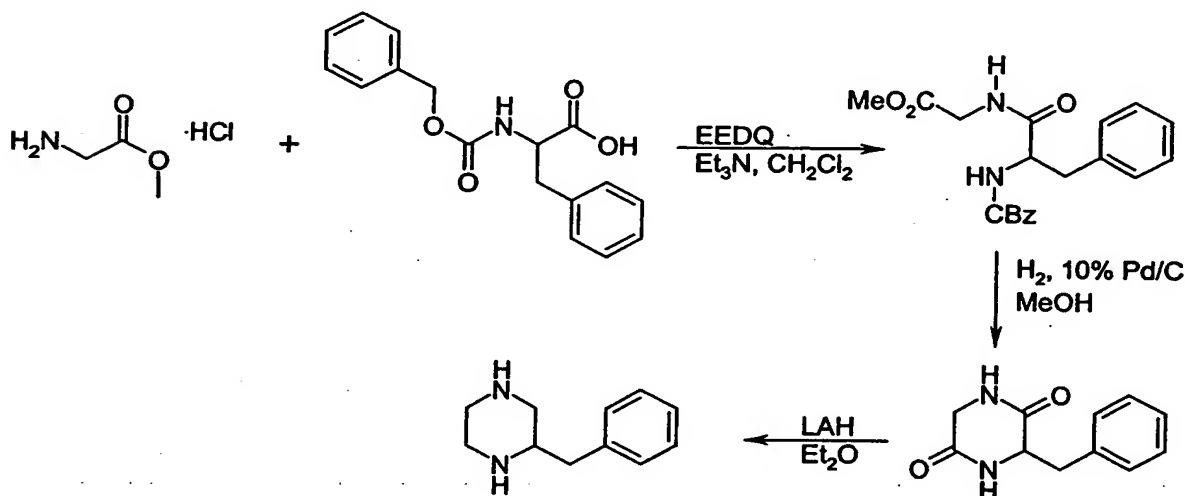
Radionuclides that are widely used in diagnostic nuclear medicine include technetium [⁹⁹Tc], iodine [¹²³I], carbon [¹¹C], and fluorine [¹⁸F]. The radiolabeled imaging agent specifically exemplified herein contains the radionuclide ¹¹C. It should be noted that the same or similar radiochemistry reactions can be carried out using radionuclides other than ¹¹C.

The invention is further illustrated by the following non-limiting examples and tabulated information. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "ml" refers to milliliters; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "LC/MS" refers to liquid chromatography mass spectrometry; "APCI" refers to atmospheric pressure chemical ionization; "mp" refers to melting point.

EXAMPLES

Example 1

Synthesis of Intermediate Substituted Piperazines



Example 1(a): Preparation of intermediate 3-benzyl-piperazine

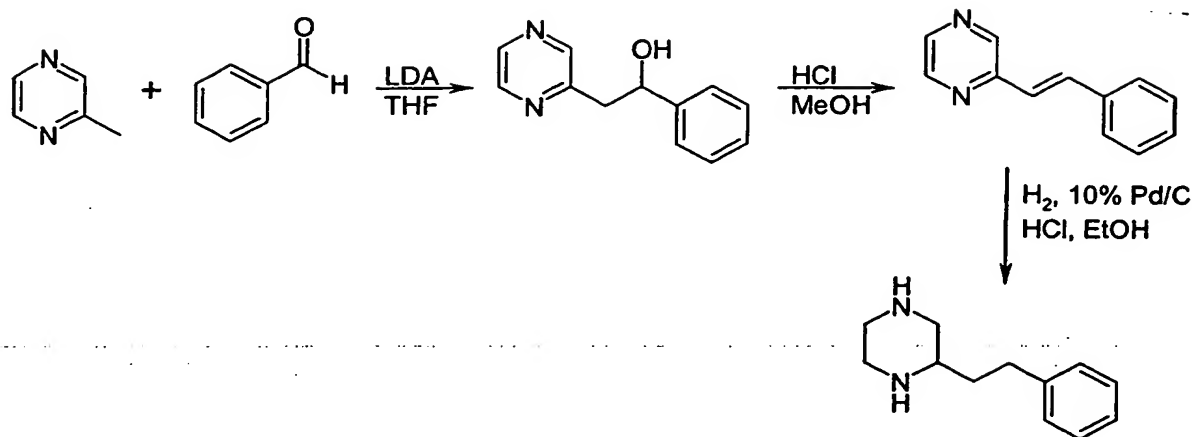
To a suspension of 3-benzyl-piperazine-2,5-dione (14.98 g, 73 mmol, prepared following generally the procedure of Halpern and Westley, J. Org. Chem. 1968, 33, 864) in dry diethyl ether (500 mL) is added dropwise to a solution of lithium aluminum hydride (400 mL of a 1 M solution in diethyl ether, 400 mmol, 5.4 eq). The suspension is heated at reflux for 23 hours and then cooled to 0 °C. Water (70 mL) is then cautiously added and the resulting suspension is warmed to room temperature. After 3 hours the suspension is filtered and the solid washed with diethyl ether (1 L). The filtrate is concentrated under vacuum to provide crude title compound (11.40 g, 88%) as a yellow, crystalline solid. A sample (2 g) is recrystallized from cyclohexane and then from toluene to provide the purified title compound (0.83 g) as a fine, white crystals: mp 80-81 °C.

Anal. Calcd. For $C_{11}H_{16}N_2$:

C, 74.96; H, 9.15; N, 15.89;

Found:

C, 74.84; H, 9.01; N, 16.15.



5

Example 1(b): To a solution of LDA (295 mL, 0.59 mol, 2 M in heptane/ THF/ ethylbenzene) in anhydrous THF (300 mL) cooled to $-40\text{ }^{\circ}\text{C}$ was added 2-methylpyrazine (48.5 mL, 0.531 mol) dropwise via an addition funnel. The reaction was allowed to warm to $-20\text{ }^{\circ}\text{C}$ and was stirred for 90 minutes when a solution of benzaldehyde (54 mL, 0.531 mol) in anhydrous THF (200 mL) was added dropwise via an addition funnel. After complete addition, the reaction was allowed to warm to room temperature and was stirred for 20 hours. The reaction was then cooled in an ice bath and saturated NH_4Cl (500 mL) was added. The resulting mixture was extracted with EtOAc (500 mL, 250 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated to a damp, beige solid. The product was triturated with Et_2O and collected then dried overnight to yield 56.0 g (53%) of a light brown solid, mp $81-84\text{ }^{\circ}\text{C}$.

15

A solution of the above-obtained solid (56.0 g, 0.28 mol) in MeOH (1.1 L) and conc. HCl (290 mL) was stirred at reflux for 24 hours. The reaction was cooled to room temperature and concentrated to a dark liquid. The dark liquid was cooled in an ice bath and water (1 L) was added. The resulting solution was neutralized with a saturated solution of Na_2CO_3 and the product was extracted with EtOAc (1 L, 2 x 500 mL). The combined extracts were dried (Na_2SO_4), filtered and concentrated to yield 46 g of a dark brown solid. The solid was purified via flash column chromatography (40% EtOAc in heptane) yielding 22.7 g of the olefin as a brown foam.

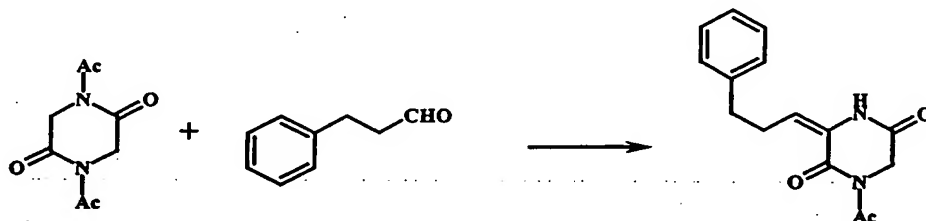
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A 1 L Parr shaker bottle was flushed with nitrogen and charged with 10% Pd/C (4.5 g, Degussa type) and the above-obtained olefin (20.0 g, 0.110 mol) in EtOH (450 mL). The reaction was hydrogenated at 50 psi for 3.5 hours when the reaction was filtered through a celite plug and rinsed with ethanol. The bottle was recharged with fresh 10% Pd/C (4.5 g,

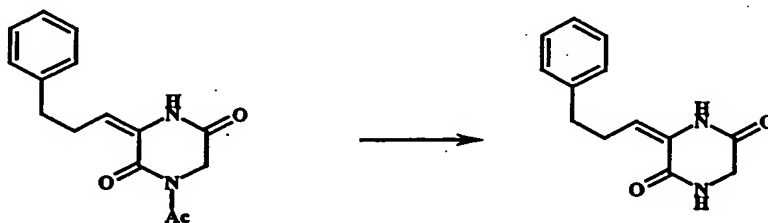
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Degussa type), the filtrate and conc. HCl (15 mL). The reaction was hydrogenated at 50 psi for 18 hours when the reaction was diluted with warm MeOH and filtered through a plug of celite. The solid was thoroughly washed with hot MeOH and the filtrate was concentrated to yield 11.2 g (39%) of the final product as the di-HCl salt, mp 297-300.

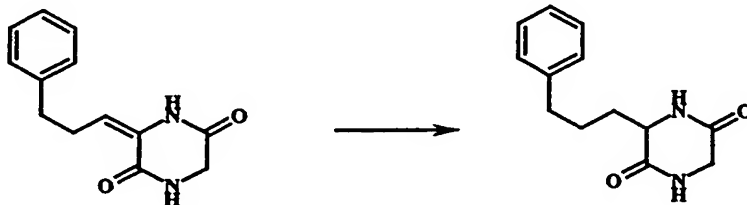
5 See: Tetrahedron, 30, 1974 pp667-673 and Tet. Lett. 1979, pp4483-4486



10 Example 1(c): DBU (14.0 g, 92 mmol) was added to a solution of the piperazine diacetate (18.2 g, 92 mmol) and aldehyde (12.3 g, 92 mmol) in 92 mL of DMF at ambient temperature. The resulting mixture was stirred at room temperature for 5h. The precipitated product was collected by filtration, providing 17.1 g of product.

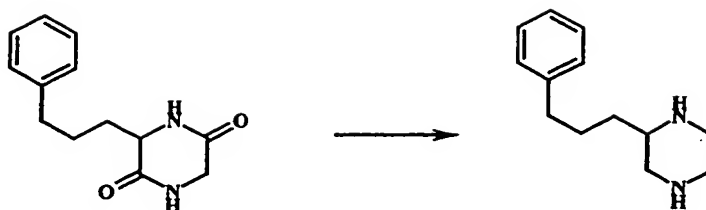


15 The monoacetate (17.0 g, 62.8 mmol) and hydrazine hydrate (9.4 g, 188.6 mmol) in 125 mL of DMF were stirred at room temperature for 20 h. The precipitated solid was collected by filtration, and washed with water and ethanol, leaving 13.7 g of product.



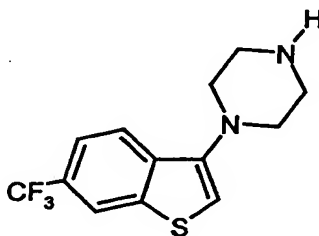
20 The olefin (13.6 g, 59.1 mmol) and palladium on carbon (2.7 g, 10% Pd/C, Degussa type, 50% H₂O) in 1.2 l of methanol were shaken on a Parr hydrogenation apparatus at 40 psi of hydrogen, until hydrogen uptake ceased. The mixture was diluted with dichloromethane and filtered through celite. Concentration of the filtrate provided 12.1 g of product.

25



A solution of LAH (156 mL, 156 mmol, 1M in THF) was added dropwise to a 0°C solution of the piperazine dione (12.1 g, 52.1 mmol) in 100 ml of THF. The mixture was heated to reflux and stirred overnight. The mixture was cooled to 0°C and 38 mL of water in 200 mL of THF was carefully added. The resulting mixture stirred for 1 h, then it was filtered, the filter cake was washed with THF, and the filtrate was concentrated in vacuo to give 7.4 g of product.

Example 2



1-(6-(trifluoromethyl)-benzo[b]thien-3-yl)-piperazine hydrochloride

2a: 2-Carbomethoxy-3-amino-6-trifluoromethylbenzo[b]thiophene:

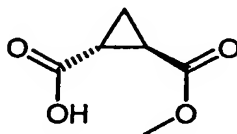
Equip a 22-L, 3-necked, round-bottom flask with a mechanical stirrer, nitrogen bubbler, and a thermocouple probe, charge with 1.20 kg (5.55 mole) of 2-nitro-4-trifluoromethylbenzonitrile, 589.3 g (496 mL, 5.55 mole) of methyl thioglycolate, and 4.3 L of NMP. Cool the resulting yellow solution to 2 °C, and add slowly, over a period of 78 min a solution prepared from 466.0 g (11.11 mole, 2.0 eq) of lithium hydroxide monohydrate in 3.36 L of water while maintaining the temperature between 2 - 20 °C. Allow the brown slurry to warm to 21 °C over a 2 h period, and then dilute with 8.0 L of water (observe exotherm-> 27 °C). Stir for 40 min and cool to 18 °C, collect the product by filtration, rinsing with 10 L of water, then air-drying at ambient temperature to give 1.295 kg (84.7% yield) of 2-carbomethoxy-3-amino-6-trifluoromethylbenzo[b]thiophene, as a light-yellow solid, 99.8% pure by HPLC assay.

2b: 1-(6-(trifluoromethyl)-benzo[b]thien-3-yl)-piperazine hydrochloride

Equip a 12-L, 3-necked, round-bottom flask with a mechanical stirrer, nitrogen bubbler, and a thermocouple probe, and charge with 1.14 kg (4.14 mole) of 2-carbomethoxy-3-

amino-6-trifluoromethylbenzo-[b]thiophene Example 2a, 196.0 g (2.28 mole, 0.55 eq) of piperazine, 4.0 L of NMP, and 570 mL of xylene. Heat the solution, and hold at 170 – 180 °C for 4 h, at which time the reaction is ca. 98% complete as determined by HPLC assay. Cool the brown solution to 168 °C, and then add 1.605 kg (18.63 mole, 4.5 eq) of piperazine (temp -> 109 °C) following with 1.575 kg (28.28 mole, 2.0 eq) of p-toluenesulfonic acid monohydrate (observe exotherm, 109 -> 130 °C). Connect a Dean-Stark trap to the condenser, and heat the reaction to collect an azeotrope. Remove a total of 410 mL of an aqueous distillate, while allowing the pot temperature to increase from 145 to 165 °C. Monitor the progress of the reaction by GC/MS and HPLC assays. After 14 h at ca. 165 °C (>99% conversion by HPLC and GC/MS assay), cool the reaction to 30-35 °C, and then quench into an extractor that contains 5 kg of ice, 12 L of water, and 8.5 L of toluene. Separate the phases, wash the organic extract with 11 L of 0.5 N NaOH, 2 L of saturated aq. NaCl., and then extract with 8 L of 1 N HCl. Dilute the acidic aqueous extract with 1 kg of ice, and basify to pH 11.2 by adding 624 g of 50% NaOH. Extract the resulting mixture with 9.5 L of toluene. Wash the toluene extract with 2 L of saturated aqueous NaCl, dry (Na₂SO₄), and filter. Charge the filtrate into a 22 L 3-necked, round-bottomed flask (N₂, mechanical stirring, temperature control probe), and add a total of 3.7 L of 1N ethereal HCl at 20 – 27 °C so that the mixture is positive to Congo Red indicator paper. During the HCl addition, add a total of 2.5 L of toluene to improve the stirring of the thick slurry that results. Stir at ambient temperature for 40 min, filter the slurry and wash with 4.5 L of toluene. After air drying, obtain 1.165 kg (87% yield) of 3-piperazinyl-6-trifluoromethyl-benzo[b]thiophene hydrochloride as a light pink-beige solid, 99.1% pure by GC/MS assay.

Example 3



3a: trans -Cyclopropane-1,2-dicarboxylic acid monomethyl ester

Suspend trans-cyclopropane-1,2-dicarboxylic acid dimethylester (59.8 g, 0.378 mol) is suspended in 1.0N phosphate buffer (1.5 L, pH=7) add pig liver esterase (2.25 mL, 7500 units), and monitor NaOH consumption with a pH meter to control the reaction. After 3 h the consumption of 189 mL of 2N NaOH indicates the complete hydrolysis of the diester to the monomethylester. Acidified the clear solution by the addition of 5N HCl to a pH=1. Separate

the enzyme by addition of dichloromethane (500 mL) and diatomaceous earth (25 g). Stir for 5 min, and then filter the mixture. Saturate the filtrate with NaCl, and extract with ethyl acetate (5 times). Combine the extracts, dry (Na_2SO_4) and evaporate to obtain 50.8 g (93%) of solid, mp 46-47°C, $m/z=145$ ($\text{M}+\text{H}$)⁺

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3b: (S,S)-(+)-Cyclopropane-1,2-dicarboxylic acid monomethyl ester

Add trans -cyclopropane-1,2-dicarboxylic acid monomethyl ester, Example 3a, (19.46 g) in acetone to quinine (43.8 g) in one portion. Heat the reaction to reflux, and then add methylcyclohexane (150 mL). After crystallization (5 times) from acetone/methylcyclohexane, collect 6.2 g of the diastereomeric salt ($\alpha_D: +173$, c: 7.3 CHCl_3)

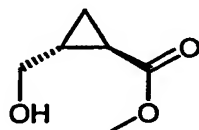
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3c: (R,R)-(-)-Cyclopropane-1,2-dicarboxylic acid monomethyl ester

Concentrate the filtrate from 3b above and treat the residue with 1N KHSO_4 solution to yield 12.0 g of the crude (R,R) enantiomer. Dissolve this material in acetone and add 1 equivalent of quinidine in one portion. Heat the reaction to reflux, and then add methylcyclohexane. After crystallization overnight, collect 10.3g of the diastereomeric salt ($\alpha_D: -235$, c: 8.5 CHCl_3)

15

Example 4



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4a: trans- 2-Hydroxymethyl-cyclopropanecarboxylic acid methyl ester

Add borane-methyl sulfide complex (177 mL, 0.354 mol), slowly, by means of a dropping funnel, to a stirring solution of trans-cyclopropane-1,2-dicarboxylic acid monomethyl ester (Example 3a) (25.5 g, 0.177 mol), trimethyl borate (60.3 mL, 0.531 mol) and tetrahydrofuran (150 mL) at 0°C. After complete addition, allow the reaction to come to ambient temperature and stir for 2 h more. Pour the reaction mixture into a stirring solution of 50% aqueous sodium chloride solution (1.5 L)-concentrated HCl (10 mL). Extract the mixture with ethyl acetate (EtOAc) (3 times), combine the extracts, dry (Na_2SO_4) and concentrate the solvent to obtain a colorless oil: 22.6 g.

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4b: (S,S)-(+)-2-Hydroxymethyl-cyclopropanecarboxylic acid methyl ester

Follow the procedure of Example 4a, and substitute (S,S)-(+)- cyclopropane-1,2-dicarboxylic acid monomethyl ester (Example 3b) therein to obtain the title compound, $\alpha_D: +54$, c: 1.5 CHCl_3 (Tetrahedron Asymmetry Vol.6, No.3, pp.683-684, 1995)

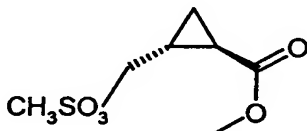
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4c: (R,R)-(-)-2-Hydroxymethyl-cyclopropanecarboxylic acid methyl ester

Follow the procedure of Example 4a, and substitute (R,R)-(-)- cyclopropane-1,2-dicarboxylic acid monomethyl ester (Example 3c) therein to obtain the title compound (α_D : -78.6, c: 4.3 CHCl_3)

5

Example 5



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5a: trans-2-Methanesulfonyloxymethyl-cyclopropanecarboxylic acid methyl ester

Add, dropwise, triethylamine (7.74 mL, 56 mmol) and 4-dimethylaminopyridine (0.013g, 0.106 mmol) in dichloromethane (30 mL) to a stirred solution of trans- 2-hydroxymethyl-cyclopropanecarboxylic acid methyl ester (Example 4a) (2.4 g, 18.64 mmol), at 0-5°C. After 0.5 h, pour the reaction mixture into water and extract the mixture with dichloromethane (3 times). Wash the combined extracts with 1N KHSO_4 , dry (Na_2SO_4) and concentrate to yield 4.29 g of a pale yellow oil, which solidifies when stored at 0°C, $m/z=209$ ($\text{M}+\text{H}$)⁺

15

5b: (S,S)-(+)-2-Methanesulfonyloxymethyl-cyclopropanecarboxylic acid methyl ester

Follow the procedure of Example 5a, and substitute (S,S)-(+)- 2-hydroxymethyl-cyclopropanecarboxylic acid methyl ester (Example 4b) therein to obtain the title compound (α_D : +75, c: 4.7 CHCl_3)

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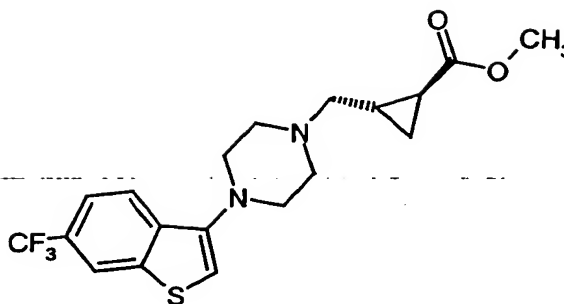
5c: (R,R)-(-)-2-Methanesulfonyloxymethyl-cyclopropanecarboxylic acid methyl ester

Follow the procedure of Example 5a, and substitute (R,R)-(-)- 2-hydroxymethyl-cyclopropanecarboxylic acid methyl ester (Example 4c) therein to obtain the title compound (α_D : -74.4, c: 5.9 CHCl_3).

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Example 6

5 6a: trans -2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid methyl ester

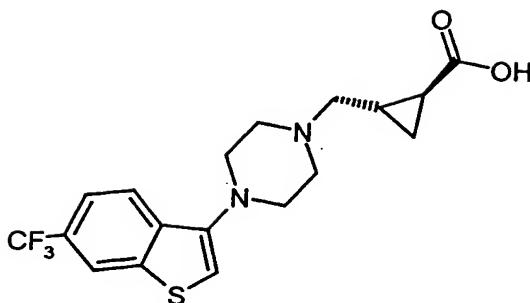
Heat at reflux for 16 h, a mixture of 1-(6-trifluoromethyl-benzo[b]thiophen-3-yl)-piperazine, free base of Example 2b, (23.0 g, 71.3 mmol), trans-2-methanesulfonyloxymethyl-
 10 cyclopropanecarboxylic acid methyl ester (Example 5a) (15.3 g, 73.5 mmol), and triethylamine (40 mL, 288 mmol) in acetonitrile (600 mL). Concentrate the reaction mixture under reduced pressure and dilute the resultant oil with EtOAc (30 mL). Filter the resulting precipitate (unreacted starting piperazine) away and purify the filtrate by column chromatography over silica gel (EtOAc/heptane/MeOH/triethylamine, 20:20:1). Concentration
 15 of the appropriate fractions gives 18.0 g of colorless oil, $m/z=413$ (M+H)⁺.

6b: (S,S)-(+)-2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid methyl ester

Follow the procedure of Example 6a, and substitute (S,S)-(+)-2-methanesulfonyloxymethyl-
 20 cyclopropanecarboxylic acid methyl ester (Example 5b) therein to obtain the title compound (α_D : +48, c: 2.8 EtOH).

6c: (R,R)-(-)-2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid methyl ester

25 Follow the procedure of Example 5, and substitute (R,R)-(-)-2-methanesulfonyloxymethyl-cyclopropanecarboxylic acid methyl ester, Example 5c, therein, to obtain the title compound (α_D : -49.3, c: 3.5 CHCl₃).

Example 7

5 7a: trans -2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid

Add 5N NaOH solution (425 mL, 226 mmol) to a solution of trans -2-[4-(6-trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid methyl ester, Example 6a, (18.0 g, 45.1 mmol) in dioxane/methanol (400 mL, 3:1) and heat the reaction at
 10 60°C for 6 h. Selectively remove most of the methanol and acidify the remaining dioxane solution to pH 5-6 with 2N acetic acid. Collect the desired compound, which precipitates from solution, to obtain 14.08 g (81%) of colorless crystals, $m/z=385$ (M+H)⁺

15 7b: (S,S)-(+)-2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid

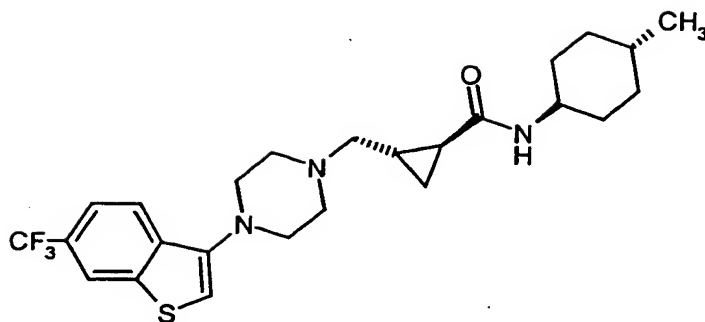
Follow the procedure of Example 7a, and substitute (S,S)-(+)-2-[4-(6-trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid methyl ester (Example 6b) therein to obtain the title compound (α_D : +55, c: 1.05 EtOH).

20 7c: (R,R)-(-)-2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid

Follow the procedure of Example 7a, and substitute (R,R)-(-)-2-[4-(6-trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid methyl ester
 25 (Example 5c) therein to obtain the title compound (α_D : -40.5, c: 0.79 CHCl₃).

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Example 8

5 8a: trans-2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid trans-(4-methylcyclohexyl)-amide

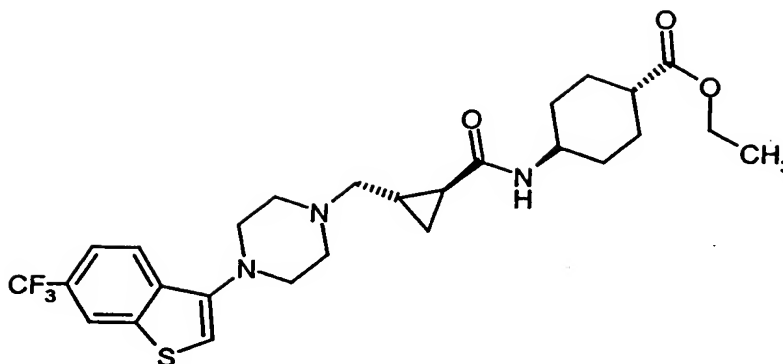
Stir a solution of trans-2-[4-(6-trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid (Example 7a) (1.99 g, 5.0 mmol), and O-[(ethoxycarbonyl)-cyanomethylenamino]-N,N,N',N'-tetramethyluronium-tetrafluoroborate (TOTU, 2.05 g, 6.3 mmol) in DMF (50 mL) at 20°C for 0.5 h. Add N-methylmorpholine (0.58 mL, 5.3 mmol), after which add trans-4-methylcyclohexylamine (1.13 g, 10 mmol), and stir the reaction for 5 h. Concentrate the reaction under reduced pressure to obtain an oil. Purify by column chromatography over silica gel (EtOAc/heptane/methanol/triethylamine, 20:20:1:1) to obtain 1.86, (76%) of colorless crystals LC/MS, $m/z = 480$ (M+H)⁺.

15 8b: (S,S)-(+)-2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid trans-(4-methylcyclohexyl)-amide

Follow the procedure of Example 8a, and substitute (S,S)-(+)-2-[4-(6-trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid (Example 7b) therein to obtain the title compound, LC/MS, $m/z = 480$ (M+H)⁺.

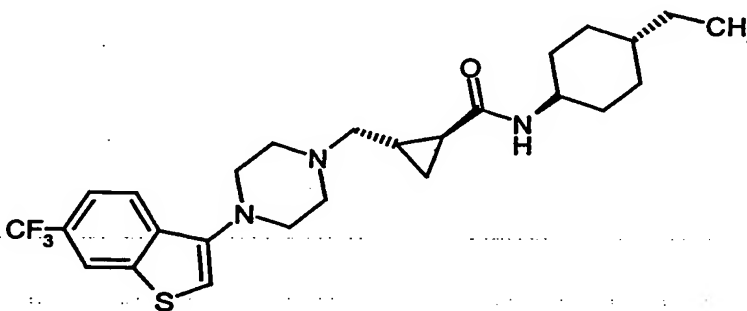
25 8c: (R,R)-(-)-2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid trans-(4-methylcyclohexyl)-amide

Follow the procedure of Example 8a, and substitute (R,R)-(-)-2-[4-(6-trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid (Example 7c) therein to obtain the title compound LC/MS, $m/z = 480$ (M+H)⁺.

Example 9

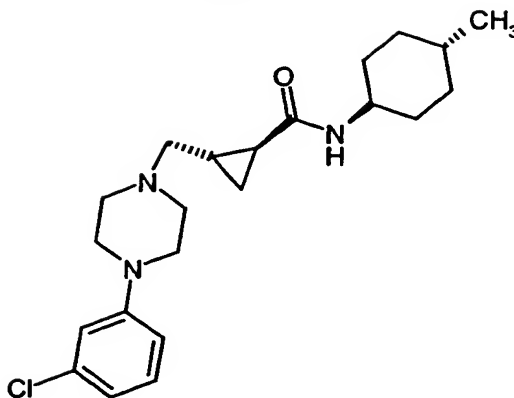
5 **trans-4-([2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarbonyl]-amino)-trans-cyclohexanecarboxylic acid ethyl ester**

Follow the procedure of Example 8a, and substitute trans-4-amino -cyclohexane carboxylic acid ethyl ester (J.Med.Chem. (1971), 14(7), 600-614) for trans-4-methylcyclohexylamine therein to obtain the title compound LC/MS, m/z= 538 (M+H)⁺.

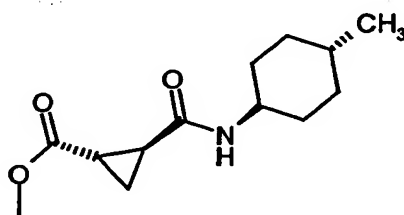
Example 10

15 **trans-2-[4-(6-Trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid trans-(4-ethylcyclohexyl)-amide**

20 Follow the procedure of Example 8a, and substitute trans-4-ethylcyclohexylamine for trans-4-methylcyclohexylamine therein to obtain the title compound LC/MS, m/z= 494 (M+H)⁺.

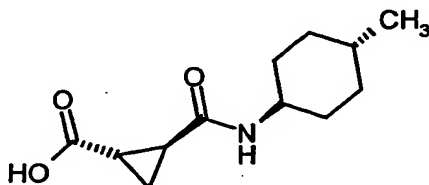
Example 11

trans-2-[4-(3-Chloro-phenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid trans-(4-methylcyclohexyl)-amide



11a: trans-2-(4-Methyl-cyclohexylcarbamoyl)-cyclopropanecarboxylic acid methyl ester

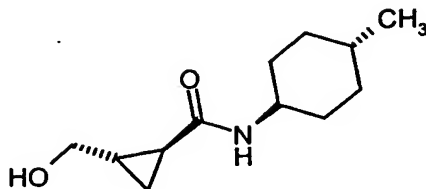
Stir a solution of trans-cyclopropane-1,2-dicarboxylic acid monomethyl ester (Example 3a) (3.0 g, 20.8 mmol) and TOTU (8.5 g, 26 mmol) in DMF (300 mL) at ambient temperature for 20 min at which time add N-methylmorpholine (2.4 mL 22.9 mmol) and trans 4-methylcyclohexylamine 3.06 g, 27.0 mmol). After 3 h, remove the solvent and dissolve the residue in H₂O/ EtOAc. Extract the aqueous layer 3 more times with EtOAc and combine the extracts. Wash the extract with saturated NaHCO₃ solution, brine and dry over MgSO₄. Concentrate the solvent to afford the crude product, and purify by column chromatography over silica gel to give 4.76 g (95%) of colorless crystals, m/z=240 (M+H)⁺.



11b: trans-2-(trans-2-Methylcyclohexylcarbamoyl)-cyclopropanecarboxylic acid

Stir a solution of trans-2-(4-methyl-cyclohexylcarbamoyl)-cyclopropane -carboxylic acid monomethyl ester (Example 11a) (4.5 g, 19.8 mmol), 5N NaOH (40 mL) and MeOH/dioxane overnight. Concentrate the reaction mixture under vacuum, cool the resulting solution and

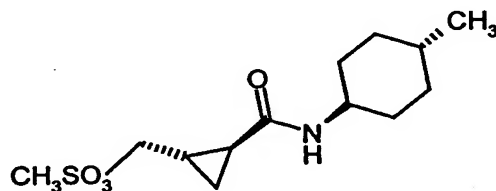
acidify to pH 5. Collect the precipitate, wash (H₂O) and dry under vacuum at 40°C to obtain 3.7 g (87%) of solid.



11c: trans-2-Hydroxymethyl-cyclopropanecarboxylic acid trans-(4-methylcyclohexyl)-amide

Stir a solution, under argon, at 0°C, of trans -2 -(trans-2-methylcyclohexylcarbamoyl)-cyclopropanecarboxylic acid (Example 11b) (3.69 g, 16.4 mmol), trimethyl borate (5.6 mL, 50 mmol), and add slowly 2N borane dimethylsulfide complex in THF (16.4 mL, 32.8 mmol).

Continue to stir the reaction at 0°C for 1 h, and then at ambient temperature for 2 h. Carefully pour the reaction mixture into ice-H₂O and acidify with 2N HCl. Extract the mixture with EtOAc (3 times), wash with brine, dry over MgSO₄ and concentrate to obtain 2.85 g (83%) of product as a solid.



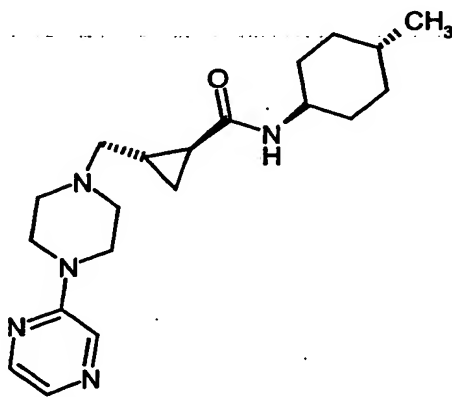
11d: Methane sulfonic acid 2-(trans-4-methyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester

Add, dropwise, to a stirring suspension at -20°C of trans-2-hydroxymethyl-cyclopropanecarboxylic acid trans-(4-methylcyclohexyl)-amide (Example 11c) (2.85 g, 13.5 mmol), triethylamine (3.74 mL, 27.0 mmol) and 4- (dimethylamino)pyridine (0.1 g, 0.82 mmol) in dichloromethane (100ml) a solution of methanesulfonic acid (1.59 mL, 20.3 mmol) in DCM (10 mL). When the reaction is complete, pour the mixture into ice water and extract the mixture with DCM. Combine the extracts, wash with 0.1N KHSO₄, brine, dry over MgSO₄ and concentrate under vacuum. Treat the residue with a mixture of isopropanol/heptane and collect the precipitate by filtration to obtain 2.91 g (74%) of solid, MS m/z = 290 (M+H)⁺.

11e: trans-2-[4-(3-Chloro-phenyl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid trans-(4-methylcyclohexyl)-amide

Reflux a solution of methane sulfonic acid 2-(trans-4-methyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester (Example 11d) (30.0mg, 0.1 mmol), 1-(3-chloro-phenyl)-piperazine hydrochloride (29.0 mg, 0.13 mmol) triethylamine (0.05 mL, 0.4 mmol) in acetonitrile (5ml) for 15 h. Concentrate the reaction mixture under vacuum and chromatograph the residue over silica gel to obtain 11.3 mg (28%) of solid, LC/MS, $m/z = 390$ (M+H)⁺.

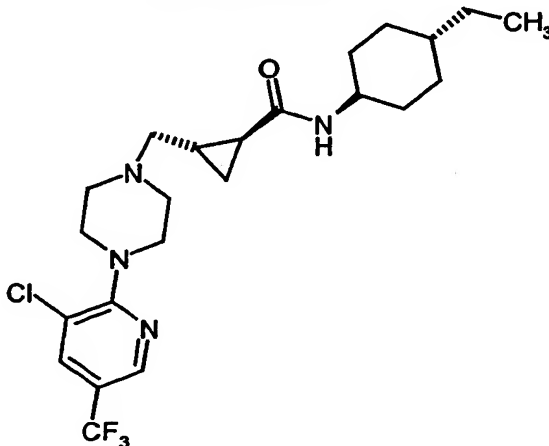
Example 12



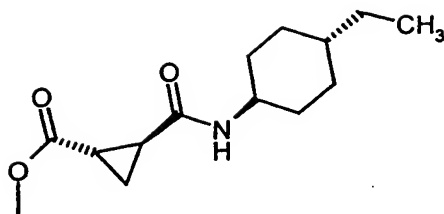
trans-2-[4-(pyrazin-2-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid trans-(4-methylcyclohexyl)-amide

Follow the procedure of Example 11e, and substitute 1-(pyrazin-2-yl)-piperazine hydrochloride for 1-(3-chloro-phenyl)-piperazine hydrochloride therein to obtain the title compound LC/MS, $m/z = 358$ (M+H)⁺.

Example 13

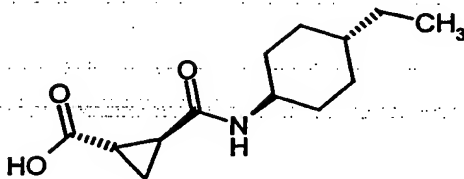


trans-2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid trans-(4-ethylcyclohexyl)-amide



13a: trans-2-(4-Ethyl-cyclohexylcarbamoyl)-cyclopropanecarboxylic acid methyl ester

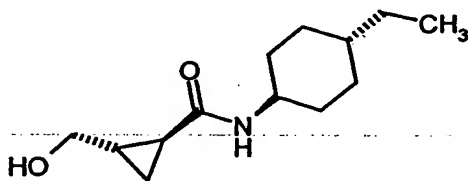
- 5 Follow the procedure of Example 11a, and substitute trans-(4-ethylcyclohexylamine) for trans-(4-methylcyclohexylamine) therein to obtain the title compound, $m/z=254$ ($M+H$)⁺.



10

13b: trans -2 -(trans-2-Ethylcyclohexylcarbamoyl)-cyclopropanecarboxylic acid

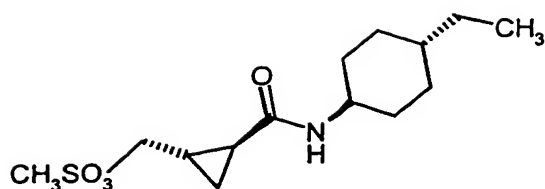
- Follow the procedure of Example 11b, and substitute trans-2-(4-ethyl-cyclohexylcarbamoyl)-cyclopropanecarboxylic acid monomethyl ester (Example 13a) for trans-2-(4-methyl-cyclohexylcarbamoyl)-cyclopropanecarboxylic acid monomethyl ester therein to obtain the
- 15 title compound.



13c: trans-2-Hydroxymethyl-cyclopropanecarboxylic acid trans-(4-ethylcyclohexyl)-amide

- 20 Follow the procedure of Example 11c, and substitute trans-2-(4-ethyl-cyclohexylcarbamoyl)-cyclopropanecarboxylic acid (Example 13b) for trans-2-(4-methyl-cyclohexylcarbamoyl)-cyclopropane carboxylic acid therein to obtain the title compound.

25



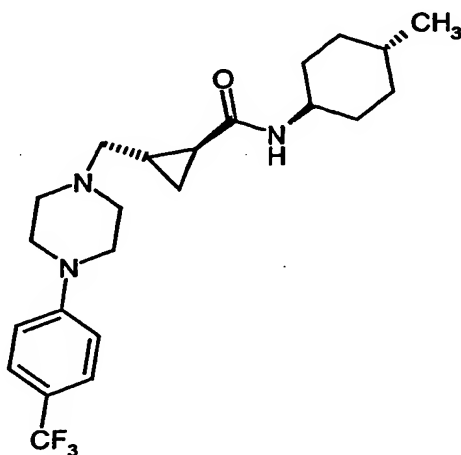
13d: Methane sulfonic acid 2-(trans-4-ethyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester

- 5 Follow the procedure of Example 11d, and substitute trans-2-hydroxymethyl-cyclopropanecarboxylic acid trans-(4-ethylcyclohexyl)-amide, Example 13c for methane sulfonic acid 2-(trans-4-methyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester therein, to obtain the title compound, $m/z=304$ ($M+H$)⁺.

10 **13e: trans-2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-ylmethyl]-cyclopropanecarboxylic acid trans-(4-ethylcyclohexyl)-amide**

- Follow the procedure of Example 11e, and substitute methane sulfonic acid 2-(trans-4-ethyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester (Example 13d) for 2-(trans-4-methyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester and 4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazine hydrochloride for 1-(3-chloro-phenyl)-piperazine hydrochloride therein to obtain the title compound LC/MS $m/z= 473$ ($M+H$)⁺.
- 15

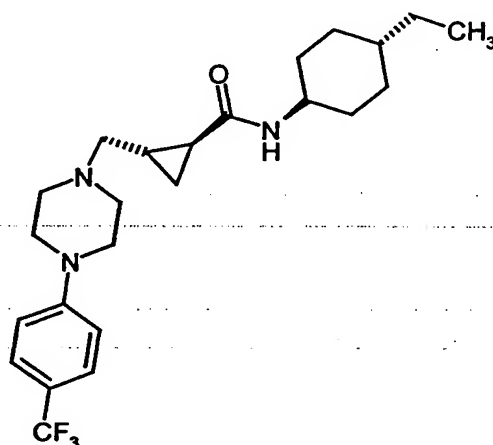
Example 14



**trans-2-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-ylmethyl]cyclopropanecarboxylic acid
trans-(4-methylcyclohexyl)-amide**

Follow the procedure of Example 11e, and substitute 1-(4-trifluoromethyl-phenyl)-piperazine hydrochloride for 1-(3-chloro-phenyl)-piperazine hydrochloride therein to obtain the title compound MS, $m/z = 424 (M+H)^+$, 85.2% pure by HPLC assay.

5

Example 15

10 **trans-2-[4-(4-Trifluoromethyl-phenyl)-piperazin-1-ylmethyl]cyclopropanecarboxylic acid
trans-(4-ethylcyclohexyl)-amide**

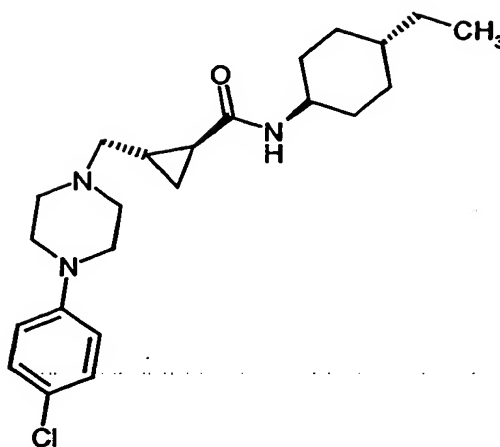
Follow the procedure of Example 11e, and substitute methane sulfonic acid 2-(trans-4-ethyl-
cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester (Example 13d) for methane sulfonic acid
15 2-(trans-4-methyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester and 4-(4-
trifluoromethyl-phenyl)-piperazine hydrochloride for 1-(3-chloro-phenyl)-piperazine
hydrochloride therein to obtain the title compound MS $m/z = 438 (M+H)^+$, 78.5% pure by
HPLC assay.

20

25

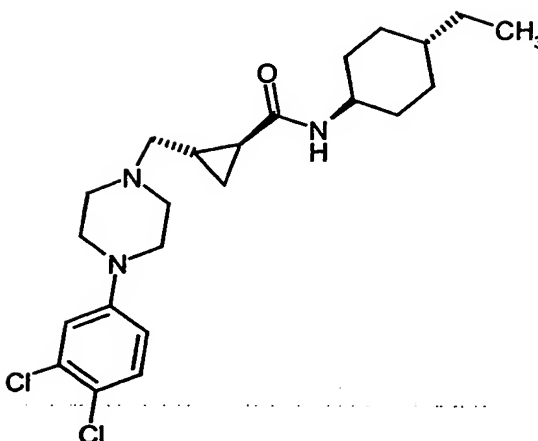
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Example 16

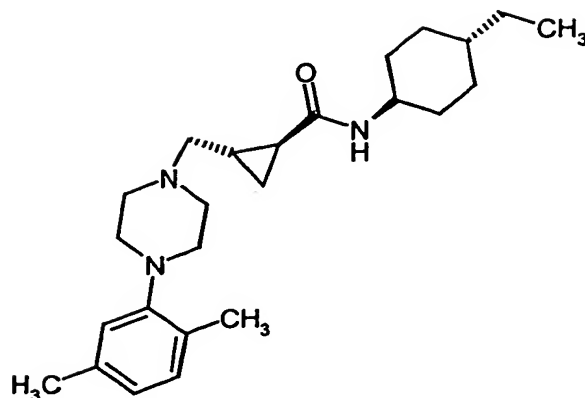
trans-2-[4-(4-Chlorophenyl)-piperazin-1-ylmethyl]cyclopropanecarboxylic acid trans-(4-ethylcyclohexyl)-amide

Follow the procedure of Example 11e, and substitute methane sulfonic acid 2-(trans-4-ethylcyclohexylcarbamoyl)-trans-cyclopropylmethyl ester, Example 13d for 2-(trans-4-methylcyclohexylcarbamoyl)-trans-cyclopropylmethyl ester and 4-(4-chlorophenyl)-piperazine hydrochloride for 1-(3-chloro-phenyl)-piperazine hydrochloride therein, to obtain the title compound LC/MS, $m/z = 404$ ($M+H$)⁺.

Example 17

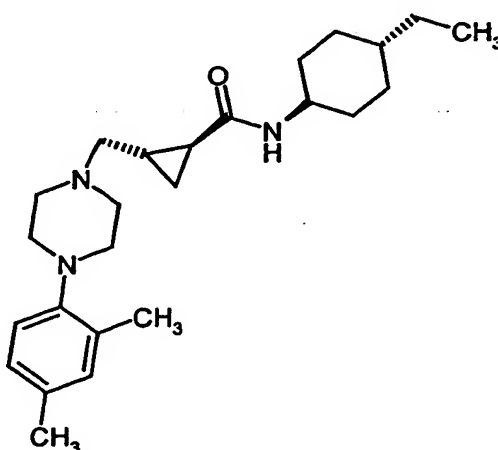
trans-2-[4-(3,4-Dichlorophenyl)-piperazin-1-ylmethyl]cyclopropanecarboxylic acid trans-(4-ethylcyclohexyl)-amide

Follow the procedure of Example 11e, and substitute methane sulfonic acid 2-(trans-4-ethylcyclohexylcarbamoyl)-trans-cyclopropylmethyl ester (Example 13d) for 2-(trans-4-methylcyclohexylcarbamoyl)-trans-cyclopropylmethyl ester and 4-(3,4-dichlorophenyl)-piperazine hydrochloride for 1-(3-chloro-phenyl)-piperazine hydrochloride therein to obtain the title compound LC/MS, $m/z = 438$ ($M+H$)⁺.

Example 18

trans-2-[4-(2,5-Dimethylphenyl)-piperazin-1-ylmethyl]cyclopropanecarboxylic acid trans-
(4-ethylcyclohexyl)-amide

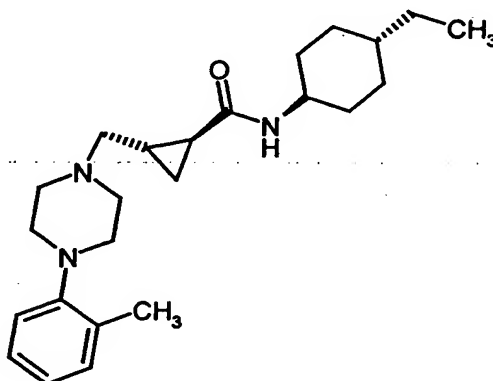
Follow the procedure of Example 11e, and substitute methane sulfonic acid 2-(trans-4-ethyl-
 cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester (Example 13d) for 2-(trans-4-methyl-
 cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester and 4-(2,5-dimethylphenyl)-piperazine
 hydrochloride for 1-(3-chloro-phenyl)-piperazine hydrochloride therein to obtain the title
 compound LC/MS, $m/z = 398$ ($M+H$)⁺.

Example 19

trans-2-[4-(2,5-Dimethylphenyl)-piperazin-1-ylmethyl]cyclopropanecarboxylic acid trans-
(4-ethylcyclohexyl)-amide

Follow the procedure of Example 11e, and substitute methane sulfonic acid 2-(trans-4-ethyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester (Example 13d) for 2-(trans-4-methyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester and 4-(2,5-dimethylphenyl)-piperazine hydrochloride for 1-(3-chloro-phenyl)-piperazine hydrochloride therein, to obtain the title compound LC/MS, $m/z = 398$ (M+H)⁺.

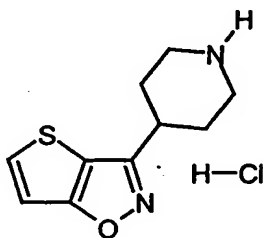
Example 20



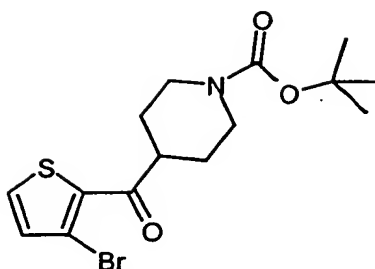
trans-2-[4-(2-Methylphenyl)-piperazin-1-ylmethyl]cyclopropanecarboxylic acid trans-(4-ethylcyclohexyl)-amide

Follow the procedure of Example 11e, and substitute methane sulfonic acid 2-(trans-4-ethyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester (Example 13d) for 2-(trans-4-methyl-cyclohexylcarbamoyl)-trans-cyclopropylmethyl ester and 4-(2-methylphenyl)-piperazine hydrochloride for 1-(3-chloro-phenyl)-piperazine hydrochloride therein to obtain the title compound LC/MS, $m/z = 384$ (M+H)⁺.

Example 21

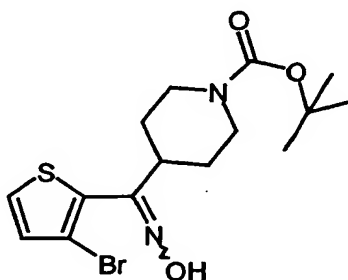


3-Piperidinyl-4-yl-thieno[2,3-d]isoxazole hydrochloride



21a: 4-(3-Bromo-thiophene-2-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester

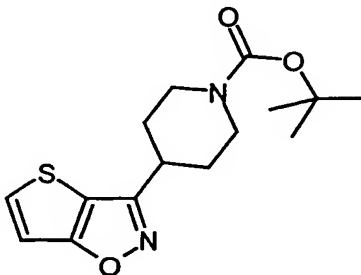
Stir a solution, under nitrogen, of 3-bromothiophene (21.0 mL, 0.224 mol) in tetrahydrofuran (1.0 L) at -78°C, and add a 2.0M solution of lithium disopropylamide in heptane/tetrahydrofuran/ethylbenzene (112 mL, 0.224 mol) for 45 min. Add, dropwise, over 2 h, a solution of 4-(N-methoxy-N-methylcarboxamido)-1-piperidinecarboxylic acid 1,1-dimethylethyl ester (prepared according to US 5,134,139) (79.4 g, 0.291 mol) in tetrahydrofuran (800 mL). Stir for 2 h, add a saturated ammonium chloride solution, and stir for an additional 0.5 h. Filter the resulting solid, and pour the filtrate into water (800 mL). Extract the aqueous mixture with ether and concentrate to obtain a dark liquid. Pour the liquid into water (400 mL), add NaCl and extract the aqueous mixture with ether. Wash the extract with water, brine, and dry over Na₂SO₄. Filter and concentrate to obtain the crude product. Chromatograph the product over silica gel (pet.ether/ether, 4:1) to obtain 41.5 g (50%) of white solid.



21b: 4-[(3-Bromo-thiophen-2-yl)-hydroxyimino-methyl]-piperidine-1-carboxylic acid tert-butyl ester

Stir a mixture of 4-(3-bromo-thiophene-2-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester (Example 21a) (41.5 g, 0.11 mol), hydroxylamine hydrochloride (15.4 g, 0.23 mol) and pyridine (190 mL) at ambient temperature overnight. Pour the reaction into water (500 mL) and extract with dichloromethane (3 times). Wash the combined extracts with saturated CuSO₄ solution (2 times), dry (MgSO₄) and concentrate to a green solid. Dissolve the solid in toluene (175 mL) and let stand at ambient temperature for 3 h. Collect the resulting crystals that form and wash with toluene (60 mL). Concentrate the filtrate and again dissolve the

residue in toluene and proceed to collect additional crystals to obtain a total yield of 25 g (58%) of the title compound as a light, green solid.



5

21c: 4-Thieno[2,3-d]isoxazol-3-yl-piperidine-1-carboxylic acid tert-butyl ester

Add to a stirring solution of 4-[(3-bromo-thiophen-2-yl)-hydroxyimino-methyl]piperidine-1-carboxylic acid tert-butyl ester (Example 21b) (25 g, 64.2 mmol) in 2-methoxyethanol (200 mL), a solution of potassium hydroxide (7.2 g, 128.4 mmol) in water (20 mL). Heat the reaction to 60°C and then add copper powder (1.25 g). Stir at 60-70°C for 6h and then at ambient temperature overnight. Pour the reaction mixture into water (500 mL) and extract with EtOAc (3 times). Concentrate to a dark residue and purify by column chromatography over silica gel (heptane/EtOAc, 4:1) to provide 9.8 g (50%) of a white solid.

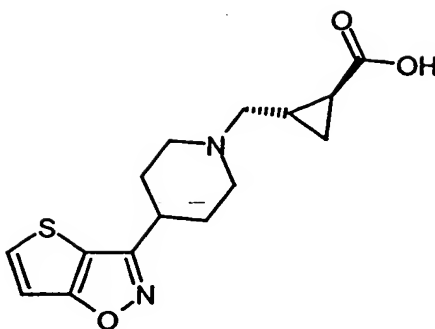
21d: 3-Piperidiny-4-yl-thieno[2,3-d]isoxazole hydrochloride

Add ethereal HCl (10 mL) to 4-thieno[2,3-d]isoxazol-3-yl-piperidine-1-carboxylic acid tert-butyl ester (Example 21c) (1.0 g, 3.2 mmol) and then methanol (1 mL) to effect solution. Permit to stand at ambient temperature for 1h and then collect 0.34 g of white solid, mp 240-241°C.

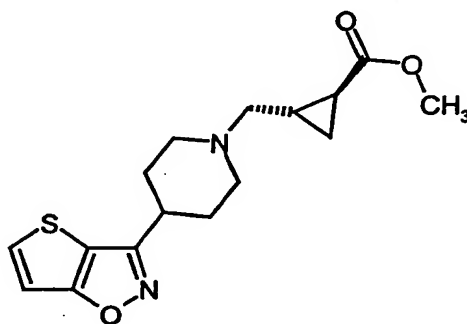
From the filtrate collect 0.25 g of additional white solid, mp 263-265°C. Both samples: MS, m/z= 209 (M+H)⁺.

Analysis (sample mp 263-265°C):

Calc. For: C ₁₀ H ₁₂ N ₂ OS·HCl:	49.08%C	5.35% H	11.45%N
Found:	49.03%C	5.29%H	11.25%N

Example 22

trans-2-(4-Thieno[2,3-d]isoxazol-3-yl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl ester



22a: trans-2-(4-Thieno[2,3-d]isoxazol-3-yl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl ester

Reflux a solution of 3-piperidinyl-4-yl-thieno[2,3-d]isoxazole trifluoroacetate, (trifluoroacetic acid salt of Example 21d) (6.0 g, 18.6 mmol), trans-2-methanesulfonyloxymethyl-cyclopropanecarboxylic acid methyl ester (Example 5a) (3.99 g, 19.2 mmol) and triethylamine (7.6 g, 75 mmol) in acetonitrile (100 mL) for 15 h. Concentrate and purify the residue by column chromatography over silica gel (dichloromethane/EtOAc/diethylamine (8:2:1). Further purify by another chromatography dichloromethane/MeOH (95:5) to obtain 1.4 g (24%) of product, MS, $m/z=321(M+H)^+$.

22b: trans-2-(4-Thieno[2,3-d]isoxazol-3-yl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl ester

Add 5N NaOH (4.4 mL, 21.9 mmol) to a solution of trans-2-(4-thieno[2,3-d]isoxazol-3-yl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl ester, Example 22a (1.4 g, 4.37 mmol) in dioxane/methanol (24 mL, 3:1), and heat to 60°C for 3 h. Concentrate the reaction

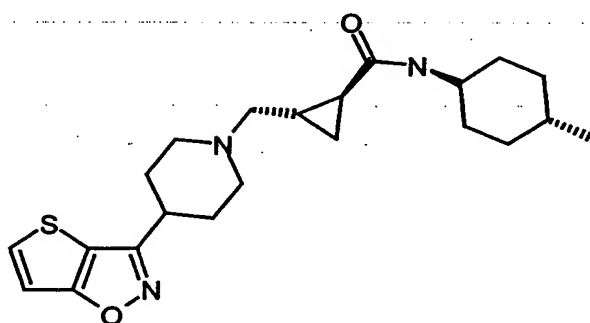
and treat the residue with acetic acid. After 36 h dilute the acetic acid solution with dichloromethane and wash the organic phase with 5% aqueous HCl, water and brine. Dry the organic phase and concentrate to a yellow oil. Evacuate the oil at high vacuum and 60°C for 20 h to obtain 0.191 g of oil.

5

Treat the aqueous washings with NaCl and collect an additional 1.0 g of the product as a solid. MS, m/z 307 ($M+H$)⁺.

Example 23

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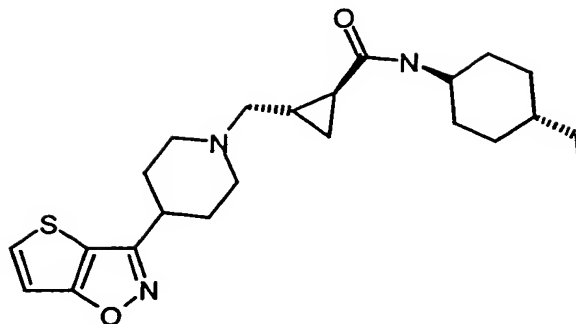
Racemic-trans-2-(4-Thieno[2,3-d]isoxazol-3-yl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid trans-(4-ethyl-cyclohexyl)-amide

15

Add TOTU (415 mg, 1.06 mmol) to a solution of trans-2-(4-thieno[2,3-d]isoxazol-3-yl-piperidin-1-ylmethyl)-cyclopropanecarboxylic acid methyl ester (Example 22b) (300 mg, 1.0 mmol), in dimethylformamide (approximately 10mL), and allow the reaction to stir at ambient temperature for 0.5 h. Add N-methylmorpholine (107 mg, 1.26 mmol) and trans-4-ethylcyclohexylamine (254 mg, 2.0 mmol), and stir for 6 h. Add additional equivalents of N-methylmorpholine and TOTU and continue to stir for overnight. I think again I didn't write it down Concentrate the reaction and purify the residue by column chromatography over silica gel (dichloromethane/MeOH, gradient 0→30%) to obtain 270 mg (65%), LC/MS, m/z = 416 ($M+H$)⁺.

25

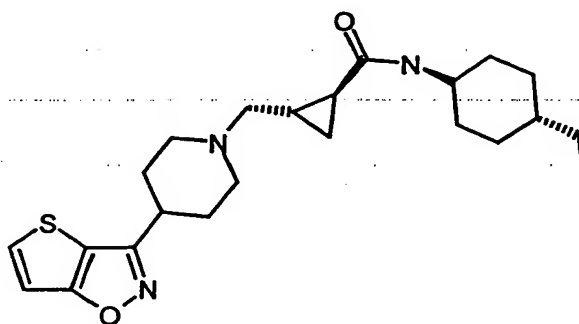
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Example 24

5 **Chiral-trans-2-(4-Thieno[2,3-d]isoxazol-3-yl-piperidin-1-ylmethyl)-
cyclopropanecarboxylic acid trans-(4-ethyl-cyclohexyl)-amide**

Dissolve racemic-trans-2-(4-thieno[2,3-d]isoxazol-3-yl-piperidin-1-ylmethyl)-
cyclopropanecarboxylic acid trans-(4-ethyl-cyclohexyl)-amide (Example 23) (14 mg) in
10 heptane/ethanol (1.5 mL, ~1:1) and make 20 separate injections of 50 μ L each on to a
preparative HPLC apparatus (Chiralpak AD 10 μ 250 x 4.6 mm, heptane/ethanol, 85:15).
Collect and combine fractions that elute at t_R = 14.2 min and obtain 3.0mg of enantiomer with
an enantiomeric excess >99%.

15

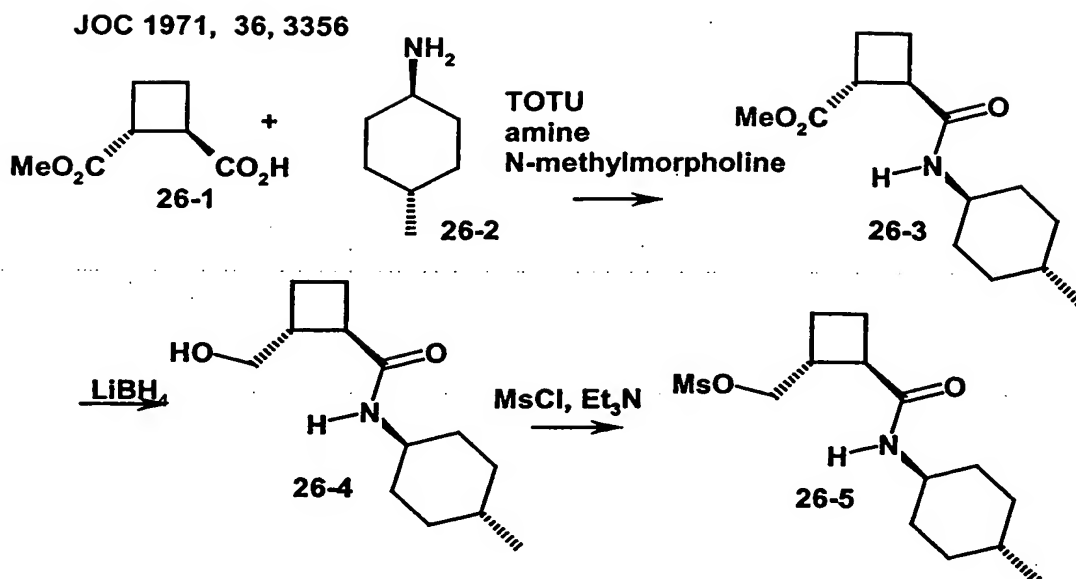
Example 25

20 **Chiral-trans-2-(4-Thieno[2,3-d]isoxazol-3-yl-piperidin-1-ylmethyl)-
cyclopropanecarboxylic acid trans-(4-ethyl-cyclohexyl)-amide**

Follow the procedure of Example 24, but collect and combine the fractions that elute at t_R =
23.6 min to obtain 6.0 mg of enantiomer with opposite chirality and an enantiomeric excess
>99%.

Example 26

5



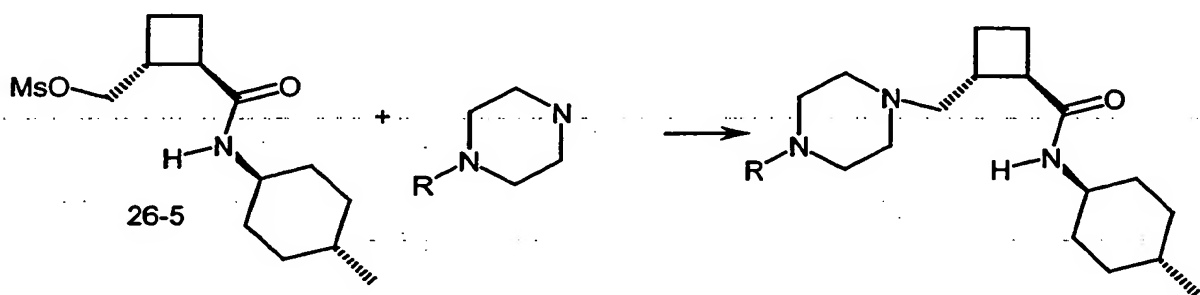
The cyclobutane carboxylic acid (26-1) (1.43 g, 9.05 mmol) and TOTU (3.7 g, 9.5 mmol) were combined in 90 mL of DMF and stirred at ambient temperature for 0.5 h. N-Methylmorpholine (0.96 g, 9.5 mmol) and the amine (26-2) (1.53 g, 13.5 mmol) were added and the mixture stirred at room temperature for 18 h. The mixture was diluted with ethyl acetate and the organic phase was sequentially washed with saturated sodium bicarbonate solution (3X), 10% HCl solution and brine (2X), then dried over magnesium sulfate, filtered and concentrated. The residue was dissolved in ethyl acetate and the mixture filtered.

Concentration of the filtrate provided 1.5 g of the product (26-3).

Lithium borohydride (93.0 mL, 5.93 mmol, 2M in THF) was added dropwise to a solution of the ester (26-3) (1.5 g, 5.93 mmol) in 20 mL of THF at ambient temperature. The solution was stirred at room temperature for 20 h, and then it was quenched by the careful addition of water. The product was extracted into ethyl acetate, and the combined organic layers were washed with water and brine, dried over magnesium sulfate, filtered and concentrated to leave 1.1 g of product. Chromatography on silica gel (40 g Biotage column) eluting with ethyl acetate and dichloromethane gave 618 mg of the alcohol (26-4).

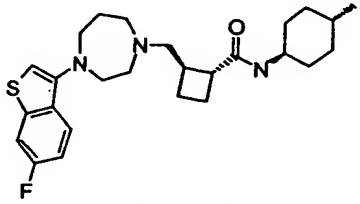
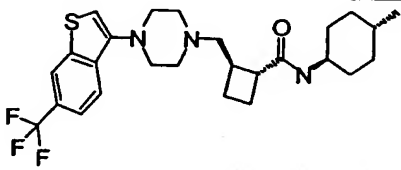
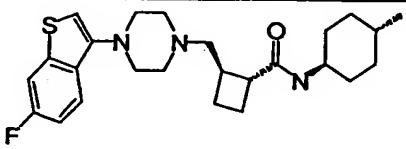
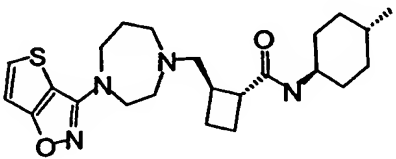
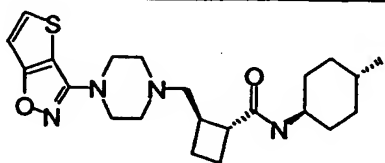
Methanesulfonyl chloride (0.276 g, 2.41 mmol) was added dropwise to a solution of the alcohol (26-4) (0.493 g, 2.19 mmol) and triethylamine (0.332 g, 3.29 mmol) in 11 mL of dichloromethane at 0°C. The mixture was stirred at 0°C for 1 h, and then it was stirred at ambient temperature for 2h. The resulting solution was diluted with dichloromethane and washed with saturated sodium bicarbonate solution, water, and brine and then filtered and the filtrate was concentrated to provide 627 mg of the product (26-5).

Scheme V



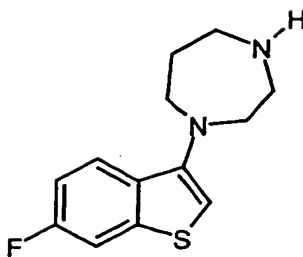
In Scheme V, R is as hereinbefore defined. For example, the mesylate (26-5) (75 mg, 0.025 mmol), potassium carbonate (52 mg, 0.038 mmol) and the amine (Example 2) (72 mg, 0.025 mmol) in 2 mL of acetonitrile were heated at 80°C in a JKEM reaction block for 20h. The mixture was cooled to room temperature, diluted with 6 mL of dichloromethane and 400 mg of polymer supported isocyanate resin was added (Argonaut Technologies, resin loading 1.49 mmol/gram) and the mixture shaken at ambient temperature for 20h. The reaction mixture was deposited on a 2g Varian strong cation exchange (SCX) column. The resin was washed twice with 4 mL ethyl acetate and thrice with 4 mL of dichloromethane. The column was further washed with 15 mL of ethyl acetate. The product was next eluted using a 4:1 mixture of 2% triethyl-amine in ethyl acetate and methanol. The volatiles were removed in vacuo and the residue was chromatographed on silica gel, eluting with methanol/ethyl acetate. Concentration of the fractions containing the product provided 67 mg of product.

The following compounds were prepared using this method.

Compound	CPD #
	829997
	829998
	829999
	830000
	829996

Characterizing data for the compounds is as follows:

CPD #	MOL WT	Amt obt	yield	basepeak	R.T. (min.)	MS% area
829997	457.65	0.051	45	458.3	1.6	100
829998	493.63	0.067	54	494..3	1.64	100
829999	443.63	0.062	56	444.3	1.57	100
830000	430.61	0.040	37	431.3	1.44	100
829996	416.59	0.052	50	417.3	1.43	100

Example 27

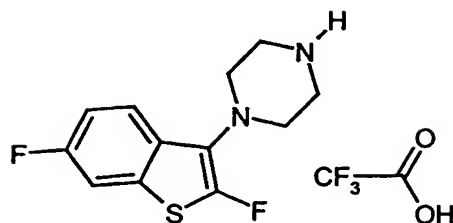
5

1-(6-Fluoro-benzo[b]thiophen-3-yl)-[1,4]diazepane**27a. 3-Amino-6-fluoro-benzo[b]thiophene-2-carboxylic acid**

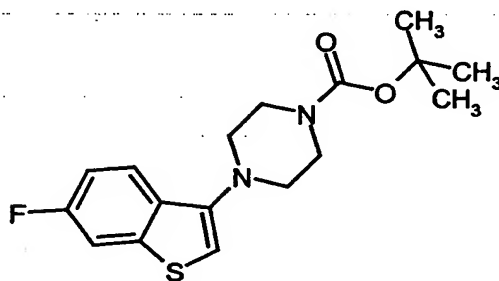
At 50°C, add to a stirring solution of 2-carbomethoxy-3-amino-6-fluoro-benzo[b]thiophene (prepared according to US 5,143,923), (90.1 g, 0.4 mol) in H₂O (450 mL), a 50% aqueous solution of NaOH (64 g, 0.8 mol) over 2-3 min. Heat the reaction to 70-73°C and continue to stir for 3 h. Add 10% aqueous isopropanol (45 mL) and bring to reflux. Remove the isopropanol under N₂ and add H₂O (300 mL). Cool the reaction mixture to between 7-10°C and add concentrated HCl (80 mL). Add H₂O (650 mL), cool to 5-7°C, filter the resulting solid, and wash the filter cake with H₂O (2x150 mL). Dry the solid under vacuum at 35°C to obtain 80.6 g (94.7%) of solid mp 160-163°C, TLC on silica gel (dichloromethane/methanol, 3:1), R_f = 0.69.

27b. 1-(6-Fluoro-benzo[b]thiophen-3-yl)-[1,4]diazepane

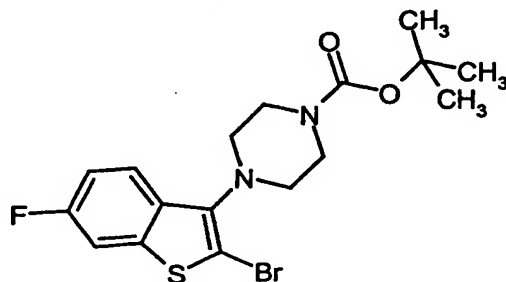
Heat a solution of 3-amino-6-fluoro-benzo[b]thiophene-2-carboxylic acid (5.0 g, 24 mmol) in 1-methyl-2-pyrrolidinone (5 ml) to 100°C for 2 h., and then, introduce a stream of nitrogen, to cool the solution to room temperature. Add homopiperazine (9.5 g, 95 mmol) and p-toluene sulfonic acid monohydrate (9.0 g, 47 mmol) and heat the mixture to 145°C for 4 h. After that time, cool the reaction mixture to room temperature, dilute with ethyl acetate (30 mL) and wash with brine (3x15 mL). Separate the organic layer and dry over Mg SO₄. Evaporate the solvent and purify the crude product by column chromatography (SiO₂, 100 g CH₂Cl₂/MeOH 9:2, then CH₂Cl₂/MeOH/NH₄OH 9:2:0.15) to give 3.9 g (65%) of yellowish oil LC/MS (LiChrospher 5 µ, RP-18, 250 mm CH₃CN/ Water-gradient 20% → 100 % (25 min), Flow: 1.5 mL/min) t_R = 10.74 min, m/z = 250.3.

Example 28

5

1-(2,6-Difluoro-benzo[b]thien-3-yl)-piperazine trifluoroacetate

- 10 **28a: 4-(6-Fluoro-benzo[b]thiophen-3-yl)-piperazine-1-carboxylic acid tert-butyl ester**
 Add a solution of di-*tert*-butyl dicarbonate (5.15 g, 23.6 mmol) in CHCl₃ (15 mL), dropwise,
 over 45 min to a solution at -65°C of 1-(6-fluorobenzo[b]thiophen-3-yl)-piperazine (prepared
 according to US 5,143,923), (2.8 g, 11.8 mmol), 4-(dimethyl-amino)pyridine (0.16, 1.3 mmol),
 and diisopropylethylamine (4.3 mL, 3.2 g, 24.8 mmol) in CHCl₃ (50 mL). Following complete
 15 addition, stir the reaction at ambient temperature for 20 h, and then pour the reaction into a
 mixture of cold (5°C) 5% aqueous NaOH/EtOAc (150/150 mL). Extract the product into
 EtOAc, wash the extract with H₂O, brine and concentrate to a red oil. Purify the crude oil
 over silica gel (EtOAc), to obtain 3.6 g, of red oil, LC/MS m/z= 337 (M+H)⁺.

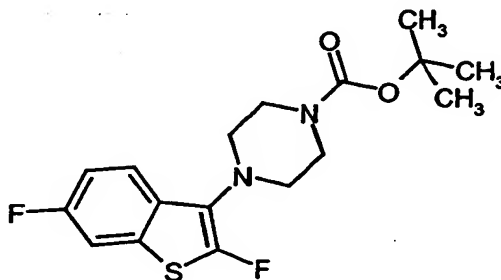


20

28b: 4-(2-Bromo-6-fluoro-benzo[b]thiophen-3-yl)-piperazine-1-carboxylic acid tert-butyl ester

Add N-bromosuccinimide (0.59 g, 3.3 mmol) to a stirring solution of 4-(6-fluoro-benzo[b]thiophen-3-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 28a) (1.00 g, 2.97 mmol) in CHCl_3 (32.8 mL) and reflux for 30 min. Allow cooling to room temperature and filter. Evaporate the solvent and purify the residue by chromatography over silica gel (EtOAc/heptane, 9:1) to obtain 0.53 g (43%) of oil, MS, $m/z = 416$ ($M+H$)⁺.

In an alternative procedure, add N-bromosuccinimide (1.319 g, 6.62 mmol) to a stirring solution of 4-(6-fluoro-benzo[b]thiophen-3-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 46a) (2.226 g, 6.62 mmol) in CCl_4 and reflux for 2 h. Allow cooling to room temperature and filter. Evaporate the solvent and purify the residue by chromatography over silica gel (EtOAc/heptane, 9:1) to obtain 2.34 g (94%) of oil.



28c: 4-(2-Fluoro-6-fluoro-benzo[b]thiophen-3-yl)-piperazine-1-carboxylic acid tert-butyl ester

At a temperature of -65°C stir, under nitrogen, a solution of the 4-(2-bromo-6-fluoro-benzo[b]thiophen-3-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 28b) (15.59 g, 37.55 mmol) in anhydrous THF (247 mL) and add, dropwise, n-butyllithium in hexane (2.5M, 19.53 mL, 48.82 mmol). Stir for 30 min and then add, dropwise, N-fluorobenzenesulfonimide (17.76 g, 56.33 mmol) dissolved in anhydrous THF. Stir overnight at ambient temperature, cool the reaction to 0°C , add saturated NaCl solution and then water. Extract the mixture with EtOAc (3x's), combine the extracts and wash with water and brine. Dry the extract (MgSO_4), and concentrate to obtain 11.0 g of oil. Chromatograph the oil over silica gel (ether/pet. ether, 9:1) and obtain 6.28 g (52%) of red oil, MS, $m/z = 354$ ($M+H$)⁺.

28d: 1-(2,6-Difluoro-benzo[b]thien-3-yl)-piperazine trifluoroacetate

Stir a solution of 4-(2-fluoro-6-fluoro-benzo[b]thiophen-3-yl)-piperazine-1-carboxylic acid tert-butyl ester (Example 28c) (250 mg, 0.70 mmol) in trifluoroacetic acid (2.2 mL) at ambient temperature for 30 min. Evaporate the trifluoroacetic acid and treat the residue with ether. Stir the suspension at ambient temperature for 2 h, and filter the resulting white solid to obtain 191 mg (56%) of the trifluoroacetate salt. MS, $m/z = 255$ ($M+H$)⁺.

Examples 29-31

The following HPLC conditions are referred to in examples 29-31:

5

HPLC Condition I:

A) 95/5/0.1% Water/Acetonitrile/Formic Acid,

B) 5/95/0.1% Water/Acetonitrile/Formic Acid.

Column: YMC ODS-A 4x50 mm, Flow rate: 2 mL/minute.

- 10 The initial HPLC conditions consisted of 100% (A) flowing at 2 mL/minute. After the initial injection a linear gradient was performed so that at 2 minutes the HPLC conditions were 100% B. These conditions were then held for 3.4 minutes at which time the system switched back to initial conditions and equilibrated for the next analysis.

15 HPLC Condition II:

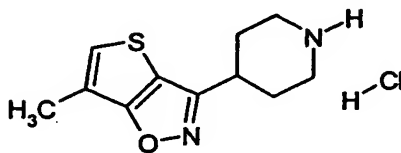
A) 95/5/0.1% Water/Acetonitrile/Formic Acid,

B) 5/95/0.1% Water/Acetonitrile/Formic Acid.

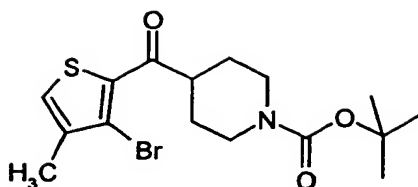
Column: YMC ODS-A 2x50 mm, Flow rate=1 mL/minute.

- 20 The initial HPLC conditions consisted of 100% (A) flowing at 0.1 mL/minute. After the initial injection a linear gradient was performed so that at 2 minutes the HPLC conditions were 100% B. These conditions were then held for 3.5 minutes at which time the system switched back to initial conditions and equilibrated for the next analysis.

25

Example 29

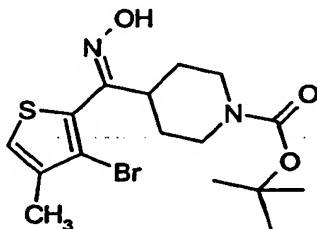
6-Methyl-3-piperidin-4-yl-thieno[2,3-d]isoxazole hydrochloride



29a: Preparation of 4-[1-(3-bromo-4-methyl-thiophen-2-yl)-methanoyl]-piperidine-1-carboxylic acid tert-butyl ester:

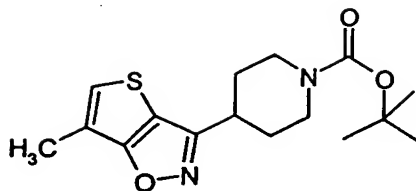
Under inert conditions, add a 2.0 M solution (in tetrahydrofuran/n-heptane) of lithium diisopropylamide (29.65 mmol, 14.83 mL, 1.05 equivalents) to a cold (-78° C) solution of 3-bromo-4-methylthiophene (28.24 mmol, 5.00 g, 1.00 equivalents) in dry tetrahydrofuran (27.33 mL). Stir at -78° C for 1 hour and add a solution of 4-(methoxy-methyl-carbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester (28.24 mmol, 7.69 g, 1.00 equivalents), dropwise. Continue stirring at -78° C for 3 hours. Quench the reaction mixture with saturated ammonium chloride (aqueous, 55 mL) and allow to warm to room temperature. Extract the reaction mixture with a mixture of ethyl acetate : diethyl ether (1 : 1, 3 times 40 mL). Combine the extracts and dry over magnesium sulfate, filter and evaporate. Purify the residue via flash column chromatography using a mixture of n-heptane : ethyl acetate (4 : 1) to yield a yellow, crystalline solid (9.84 g).

MS (CI, methane) m/e 388 (MH⁺), LC/MS (APCI), m/e 288 (M-100), retention time 2 min. 43 sec. Condition I.



29b: Preparation of 4-[1-(3-bromo-4-methyl-thiophen-2-yl)-1-hydroxyimino-methyl]-piperidine-1-carboxylic acid tert-butyl ester:

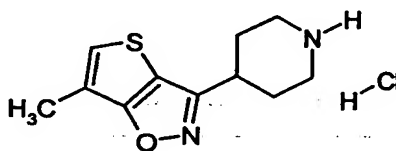
Add ammonium hydroxide hydrochloride (50.68 mmol, 3.52 g, 2.00 equivalents) to a stirred solution of 4-[1-(3-bromo-4-methyl-thiophen-2-yl)-methanoyl]-piperidine-1-carboxylic acid *tert*-butyl ester (25.54 mol, 9.84 g, 1.00 equivalents) in pyridine (47.5 mL). Stir at room temperature overnight and at 70° C for 4 hours. Cool the reaction mixture and add hydrochloric acid (3 M solution, 115 mL). Extract the reaction mixture with dichloromethane (115 mL), filter the organic layer, wash with water (100 mL), dry over magnesium sulfate, filter and evaporate. Recrystallize the resulting residue from toluene to yield a white solid (4.84 g). LC/MS (APCI), m/e 403 (MH⁺), retention time 2 min. 32 sec. Condition I.



29c: Preparation of 4-(6-methyl-thieno[2,3-d]isoxazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester:

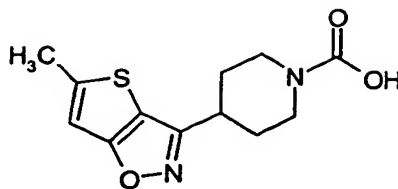
Add cesium carbonate (3.72 mmol, 1.21 g, 1.50 equivalents) and copper iodide (0.25 mmol, 47 mg, 0.10 equivalents) to a stirred solution of 4-[1-(3-bromo-4-methyl-thiophen-2-yl)-1-hydroxyimino-methyl]-piperidine-1-carboxylic acid tert-butyl ester (2.48 mmol, 1.00 g, 1.00 equivalents) in 2-methoxy ethanol (25 mL). Stir the resulting mixture at room temperature overnight and filter to remove the inorganic material. Concentrate the filtrate and partition the resulting oil between ethyl acetate (75 mL) and water (25 mL). Extract the aqueous layer with ethyl acetate (2 x 75 mL) and wash the combined organic layers with saturated sodium chloride (aqueous, 25 mL), dry over magnesium sulfate, filter and evaporate. Purify the residue via flash column chromatography eluting with n-heptane : ethyl acetate (4 : 1) to yield a white solid (588 mg). MS (CI, methane) m/e 323 (MH⁺), LC/MS (ESI), m/e 345 (MNa⁺), retention time 2.05 minutes. Condition II.

29d: Preparation of 6-methyl-3-piperidin-4-yl-thieno[2,3-d]isoxazole hydrochloride:

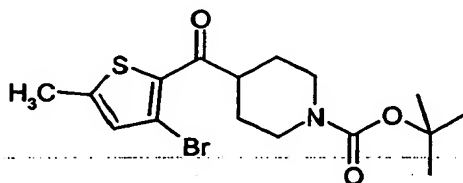


Stir a solution of 4-(6-methyl-thieno[2,3-d]isoxazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester (8.84 mmol, 2.85 g, 1.00 equivalents) in hydrochloric acid (48.75 mL, 1 M solution in diethyl ether) and methanol (2.00 mL) at room temperature for 3.5 hours. Filter the suspension, collect the white solid and dry to yield the desired product (659 mg). Allow the mother liquor to age overnight, filter, collect the white solid and dry to yield additional desired product (1.252 g). LC/MS (ESI), m/e 223 (MH⁺), retention time 1.14 minutes. Condition II.

Example 30



4-(5-Methyl-thieno[2,3-d]isoxazol-3-yl)-piperidine-1-carboxylic acid:

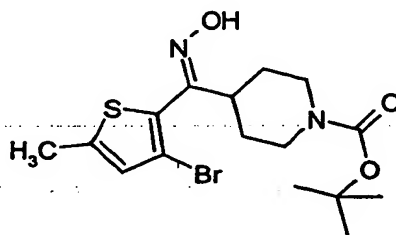


5

30a: Preparation of 4-[1-(3-bromo-5-methyl-thiophen-2-yl)-methanoyl]-piperidine-1-carboxylic acid tert-butyl ester:

Prepared essentially as in 29a except that 2-bromo-5-methyl thiophene is used as the starting material. In addition, 1.20 equivalents of lithium diisopropylamide and 1.24 equivalents of 4-(methoxy-methyl-carbamoyl)-piperidine-1-carboxylic acid *tert*-butyl ester are used for the reaction. Accordingly, stirring time of the reaction mixture may vary. Purification of the residue via flash column chromatography uses a gradient with a mixture of ethyl acetate : n-heptane (1 : 9) to ethyl acetate : n-heptane (2 : 8) to yield a yellow oil. LC/MS (ESI), m/e 332 (M-56) and 388 (MH⁺), retention time 2.15 minutes. Condition II.

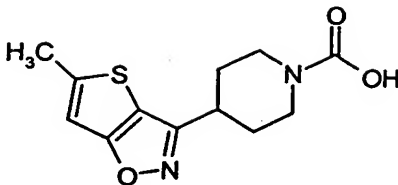
15



30b: Preparation of 4-[1-(3-bromo-5-methyl-thiophen-2-yl)-1-hydroxyimino-methyl]-piperidine-1-carboxylic acid tert-butyl ester:

Prepared essentially as 29b except that 4-[1-(3-Bromo-5-methyl-thiophen-2-yl)-methanoyl]-piperidine-1-carboxylic acid *tert*-butyl ester is used as the starting material and the reaction mixture was stirred at 70° C for 6 hours. LC/MS (ESI), m/e 347 (M-56) and 403 (MH⁺), retention time 2.03 minutes. Condition II.

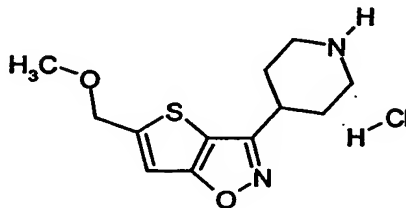
20



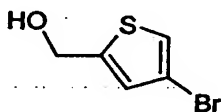
30c: Preparation of 4-(5-methyl-thieno[2,3-d]isoxazol-3-yl)-piperidine-1-carboxylic acid:

Prepared essentially as in 29c except that 4-[1-(3-bromo-5-methyl-thiophen-2-yl)-1-hydroxyimino-methyl]-piperidine-1-carboxylic acid tert-butyl ester is used as the starting material. Two other differences are: 1) 0.05 equivalents of copper iodide is used, and 2) no partition between ethyl acetate and water accompanied by subsequent extraction with ethyl acetate is required. Purification of the residue via flash column chromatography uses a mixture of ethyl acetate : n-heptane (1 : 4) to yield a white solid. LC/MS (ESI), m/e 345 (MNa⁺), retention time 2.12 minutes. Condition II.

Example 31

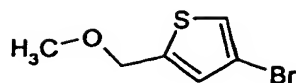


5-Methoxymethyl-3-piperidin-4-yl-thieno[2,3-d]isoxazole hydrochloride



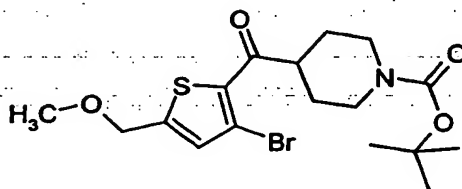
31a: Preparation of (4-bromo-thiophen-2-yl)-methanol:

Under inert conditions, add sodium borohydride (13.82 mmol, 0.523 g, 2.08 equivalents) in absolute ethanol (16 mL) dropwise over a period of 15 minutes to a stirred mixture of 4-bromothiophene-2-carboxaldehyde (26.58 mmol, 5.08 g, 1.00 equivalents) in cold (0° C) absolute ethanol (32 mL). Stir the resulting mixture at room temperature for 2.5 hours and add glacial acetic acid dropwise until the effervescence ceases. Evaporate the resulting solution, take the residue up in diethyl ether (75 mL), wash with water (15 mL) and brine (15 mL) and dry over magnesium sulfate. Filter and evaporate to yield the product as a colorless oil (5.13 g).



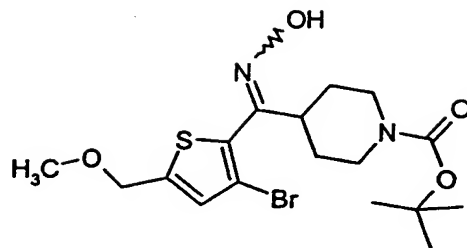
31b: Preparation of 4-bromo-2-methoxymethyl-thiophene:

Add sodium hydride (737 mg, 29.23 mmol, 1.10 equivalents, 95%) to a solution containing methyl iodide (1.65 mL, 26.57 mmol, 1.00 equivalents) and (4-bromo-thiophen-2-yl)-methanol (5.13 g, 26.57 mmol, 1.00 equivalents) in tetrahydrofuran (dry, 25 mL). Stir the resulting mixture at room temperature overnight and evaporate. Partition the residue between water (100 mL) and dichloromethane (100 mL). Extract the aqueous layer with dichloromethane (100 mL), combine the organic layers, dry over magnesium sulfate, filter and evaporate to yield the desired product as a yellow oil.



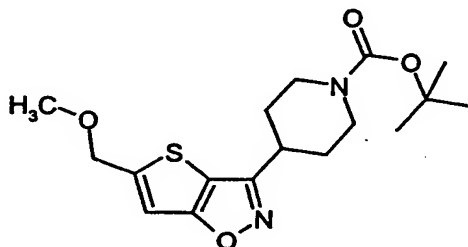
31c: Preparation of 4-[1-(3-bromo-5-methoxymethyl-thiophen-2-yl)-methanoyl]-piperidine-1-carboxylic acid tert-butyl ester:

Add lithium diisopropyl amide (13.20 mL, 26.37 mmol, 1.05 equivalents) to a stirred, cold (-78° C) solution of 4-bromo-2-methoxymethyl-thiophene (5.20 g, 25.11 mmol, 1.00 equivalents) in tetrahydrofuran (dry, 24.30 mL). Stir at -78° C for 1 hour and add a solution of 4-(methoxy-methyl-carbamoyl)-piperidine-1-carboxylic acid tert-butyl ester (6.84 g, 25.11 mmol, 1.00 equivalents) in tetrahydrofuran (dry, 16.40 mL), dropwise. Stir the resulting solution at -78° C for 3 hours. Quench the reaction mixture with saturated sodium chloride (aqueous, 50 mL). Allow the resulting mixture to warm to room temperature and extract with a mixture of ethyl acetate : diethyl ether (1 : 1, 3 x 35 mL). Combine the extracts, dry over magnesium sulfate, filter and evaporate. Purify the residue via flash column chromatography eluting with a mixture of n-heptane : ethyl acetate (4 : 1) to yield the desired product as a yellow oil (9.47 g). LC/MS (ESI), m/e 362 (M-56) and 418 (MH⁺), retention time 2.08 minutes. Condition II.



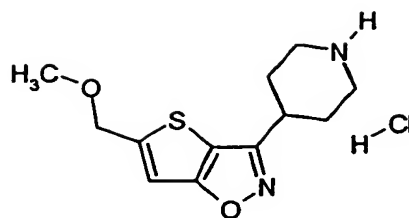
31d: Preparation of 4-[1-(3-bromo-5-methoxymethyl-thiophen-2-yl)-1-hydroxyimino-methyl]-piperidine-1-carboxylic acid tert-butyl ester:

5 Add hydroxylamine hydrochloride (2.29 g, 45.27 mmol, 2.00 equivalents) to a stirred solution of 4-[1-(3-bromo-5-methoxymethyl-thiophen-2-yl)-methanoyl]-piperidine-1-carboxylic acid tert-butyl ester (9.47 g, 22.64 mmol, 1.00 equivalents) in pyridine (42.40 mL). Stir the resulting solution at room temperature overnight and then at 70° C for 4 hours. Cool the reaction mixture slightly, add hydrochloric acid (3N, 100 mL) and extract the resulting mixture with dichloromethane (100 mL). Wash the extract with water (100 mL), dry over magnesium sulfate, filter and evaporate to yield the desired product as a yellow oil (9.48 g).



31e: Preparation of 4-(5-methoxymethyl-thieno[2,3-d]isoxazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester:

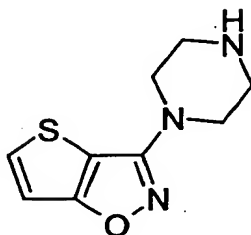
15 Add cesium carbonate (1.13 g, 3.46 mmol, 1.50 equivalents) and copper iodide (44 mg, 0.23 mmol, 0.10 equivalents) to a stirred solution of 4-[1-(3-bromo-5-methoxymethyl-thiophen-2-yl)-1-hydroxyimino-methyl]-piperidine-1-carboxylic acid tert-butyl ester (1.00 g, 2.31 mmol, 1.00 equivalents) in 2-methoxy ethanol (23.30 mL). Stir the resulting mixture at room temperature overnight or up to 3 days and filter through celite. Evaporate the filtrate, partition the residue between ethyl acetate (70 mL) and water (23 mL) and separate. Extract the aqueous layer with ethyl acetate (3 x 70 mL), combine the organic layers, dry over magnesium sulfate, filter and evaporate. Purify the residue via flash column chromatography eluting with a mixture of hexane : ethyl acetate (4 : 1) to yield the desired product as a yellow oil. LC/MS (ESI), m/e 375 (MNa⁺), retention time 1.98 minutes. Condition II.



31f: Preparation of 5-methoxymethyl-3-piperidin-4-yl-thieno[2,3-d]isoxazole hydrochloride:

Stir a solution of 4-(5-methoxymethyl-thieno[2,3-d]isoxazol-3-yl)-piperidine-1-carboxylic acid tert-butyl ester (2.21 g, 6.68 mmol, 1.00 equivalents) and hydrochloric acid (1.0 M in diethyl ether, 35 mL) overnight to form a suspension. Add additional hydrochloric acid (1.0 M in diethyl ether, 10 mL). Stir the suspension overnight, filter and wash the solid with ether. Collect the solid and dry to yield the desired product as a dark blue solid. LC/MS (ESI), m/e 253 (MH^+), retention time 1.17 minutes. Condition II.

Example 32



Synthesis of BOC protected piperazine-thienylisoxazole

3-Bromothiophene-2-carbaldehyde oxime

3-Bromothiophene-2-carbaldehyde (Maybridge) (28.7gm, 0.15 mol) in ethanol (50ml) was added in one portion to a solution of hydroxylamine hydrochloride (13.8 gm, 0.2 mole), sodium hydroxide (8 gm, 0.2 mol) in water (30ml) and ethanol (100 ml). The mixture was stirred at 0°C for 2 hours and was kept at 0°C overnight. The reaction mixture was diluted with cold water (600 ml), and the precipitated solids were collected by filtration to provide 20.5 gm, (67%) of product. The aqueous layer was further extracted with ethyl acetate and, the combined organic layers were washed with brine, dried with magnesium sulfate filtered and concentrated in vacuo to leave an additional 6.9g of product.

3-bromothiophene-2-hydroximidoyl chloride

To a solution of 3-bromothiophene-2-carbaldehyde oxime (10.8gm, 52.4 mmol), hydrogen chloride (14.5ml, 4M in dioxane) in DMF (100ml) was added oxone (16.9gm, 1.05 equiv) in one portion at room temperature. The mixture was stirred at ambient temperature overnight.

At the end of the reaction, DMF solution was poured into water and product was extracted into ethyl acetate. The organic solution was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo to 12.68gm of product which was used in the next reaction without further purification.

5

(4-t-Butoxycarbonylpiperazinyl)-3-bromo-2-thienyl methanone oxime

3-bromothiophene-2-hydroximidoyl chloride (16.4gm, 68 mmol) in tetrahydrofuran (THF, 70ml) was added dropwise to a solution of N-(t-butoxycarbonyl)piperazine (14gm, 1.1 equiv.), DABCO (9.5gm, 1.25equiv.) in DMF (100ml) at 0°C over 25 minutes. The mixture was stirred for 3.5 hrs. At the end, the mixture was poured into water and was extracted with ethyl acetate. The organic was washed with brine and dried over magnesium sulfate. The solvent was removed on a rotary evaporator. The crude product (30.5gm) was purified by chromatography on a Biotage cartridge (400gm of silica gel), eluting with methanol in dichloromethane (0-5 % of MeOH). The product thus obtained weighed 24.6 gm (85%).

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(t-BOC-piperazine)-3-thienylbenzisoazole

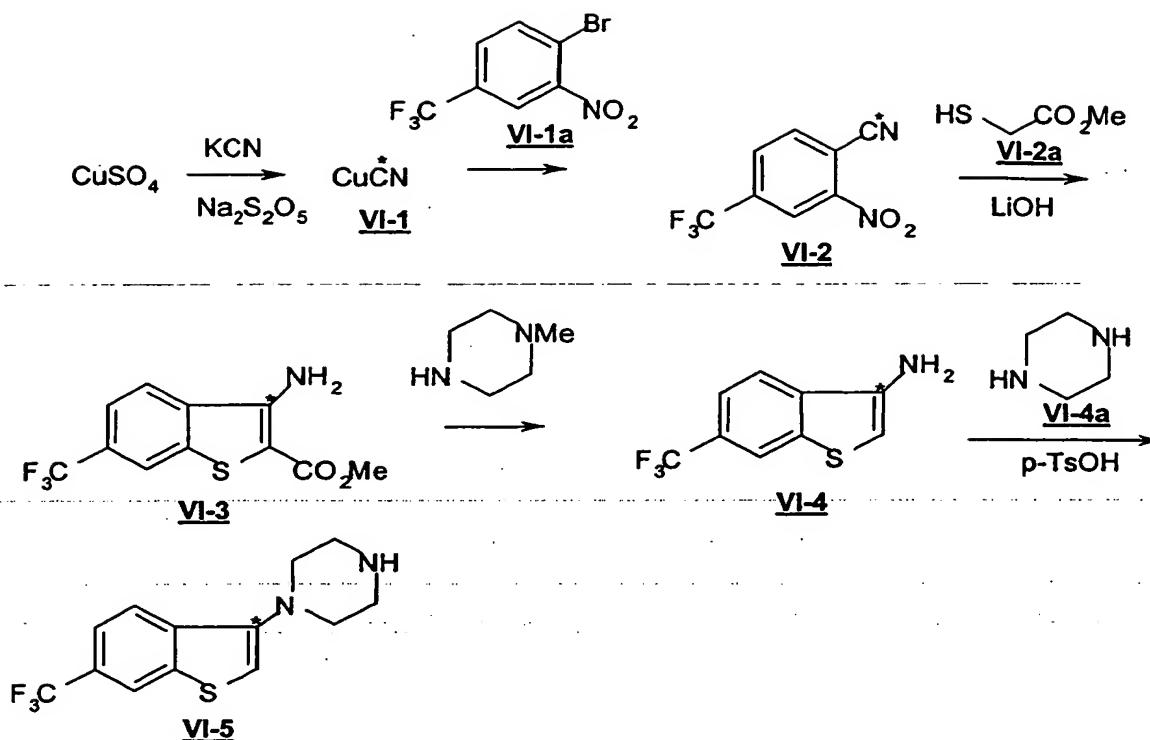
A mixture of (4-t-Butoxycarbonylpiperazinyl)-3-bromo-2-thienyl methanone oxime (10.3gm, 26.4 mmol), cesium carbonate (10.7gm, 32.7mmol), and copper iodide (500mg) in methoxyethanol (200ml) was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate, the washed with water. The aqueous solution was extracted three times with ethyl acetate. The organic solution (total 600ml) was washed with brine and was dried over magnesium sulfate then concentrated to an oil (~10gm). This material was purified by chromatography using a Biotage cartridge (120gm of silica gel, eluting with 0-8% Methanol in dichloromethane). The product thus obtained as light oil (5.1gm, 62%).

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Example 33

Synthesis of radiolabeled C14 intermediate useful for the preparation of certain compounds within the scope of the present invention.

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General: Analytical thin layer chromatography (TLC) was performed on E. Merck TLC plates with silica gel 60 F₂₅₄ (0.25 mm). TLC plates used in the analysis of radioactive samples were scanned on a BIOSCAN system 2000 Imaging Scanner using P-10 gas (10% methane, 90% argon). Identity of the intermediates was established by co-migration in radio-TLC and/or radio-HPLC with the standard samples of unlabeled analogues. Flash chromatography was performed using silica gel with a particle size of 40-63 μm . Specific activity was determined on a Packard Minaxi Tri-Carb Liquid Scintillation Analyzer (Model 1600 TR) using Bio-Safe II as scintillation cocktail.

Purification of compounds VI-2, VI-3, VI-4, VI-5, and VI-6 was monitored by HPLC (conditions:A) which was carried out on Waters 600 Controller, Waters 996 Photodiode Array Detector, Millennium Chromatography Manager and Beta-Ram Radioactive Flow Through Monitor System, Model 2 (IN/US Systems Inc.). Final purity determination of VI-7 by HPLC (conditions:B) was performed on Waters Model 510 Pumps, Waters 680 Gradient Controller, Waters 715 Ultra Wisp Autosampler, Waters 484 Tunable Absorbance Detector and Beta-Ram Radioactive Flow-Through Monitor System, Model 2 (IN/US Systems Inc.).

Conditions A: YMC Basic 5 μm , C18, 4.6x250 mm, mobile phase A: (v/v) 50/50 acetonitrile/0.1N ammonium formate, mobile phase B: (v/v) 75/25 acetonitrile/0.1N ammonium formate, flow rate 1.0 mL/min, uv detection at 254 nm.

Gradient:	Time (minutes)	%MP:A	%MP:B
	0	100	0
	15	100	0
5	25	0	100
	30	0	100
	35	100	0

Conditions B: Ultremex 5 μ m, C8, 4.6 x 150 mm, mobile phase (v/v/v) 50/50/0.25 acetonitrile/0.05 M potassium phosphate buffer, pH 3.0/triethylamine, flow rate 1.0 mL/min, uv detection at 210 nm.

[¹⁴C] Copper (I) Cyanide (VI-1):

A solution of copper (II) sulfate pentahydrate (4.16 g, 16.67 mmol) in water (13.3 mL) was heated to 70 °C and a solution of sodium metabisulfite (1.94 g, 6.28 mmol) in water (3.3 mL) at 70 °C was added in one minute. Immediately a solution of [¹⁴C] potassium cyanide (245.5 mg, 200 mCi, 3.77 mmol, S.A. 53.0 mCi/mmol) and unlabeled potassium cyanide (0.84g, 12.9 mmol) in water (3.3 mL) at 70 °C was added in one minute. A white solid precipitated out of solution and blue color of the solution was discharged. After stirring for 10 min at 70 °C, the mixture was filtered hot and the solid was washed with hot water (15mL) and ethanol (15mL). The white solid was dried under vacuum (0.1 mm Hg) for 27 h 45 min to give VI-1 (1.393 g, 186.6 mCi) in 93.3% yield.

2-Nitro-4-(trifluoromethyl)-[7-¹⁴C]benzonitrile (VI-2):

To a suspension of [¹⁴C]copper (I) cyanide (VI-1) (1.393 g, 15.55 mmol, 186.6 mCi) in 1-methyl-2-pyrrolidinone (NMP, 10mL) was added 4-bromo-3-nitrobenzotrifluoride (6.33 g, 23.45 mmol) and the mixture was heated at 190-195 °C for 1 h. Ethyl acetate (25mL) and water (20 mL) were added at room temperature and the mixture was filtered through celite. To the filtrate more water (20mL) and ethyl acetate (25mL) were added and the aqueous layer was extracted with ethyl acetate (90mL). The organic extract was washed with iron (III) chloride solution (50mL) prepared by dissolving iron (III) chloride (7.468 g, 46.04 mmol) in water (50 mL). The organic extract was further washed with water (30mL), sat. sodium chloride (15mL), dried (Na₂SO₄) and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 9/1-7/3) to provide an oil which was dissolved in hexane (70 mL). The solvent was removed under reduced pressure and residue was dried under vacuum for 15 h 40 min to provide VI-2 (3.01 g, 167.13 mCi, 89.6% yield) as a yellow solid. Radio-TLC (hexane/ethyl acetate, 9/1), R_f=0.21; HPLC (System A), RCP 99.86% (ret. time, 9.2 min).

[3-¹⁴C]-3-Amino-2-carbomethoxy-6-trifluoromethylbenzo[b]thiophene (VI-3):

Nitrile (VI-2) (3.01g, 13.9 mmol, 167.13mCi) was dissolved in DMF (14mL) and methyl thioglycolate (1.78g, 15.94 mmol, 95%) was added in one minute. The mixture was cooled to 0-5 °C and a solution of lithium hydroxide (0.689 g, 28.77 mmol) in water (9.2mL) was added dropwise in 12 minutes. After the addition, cooling bath was removed and the mixture was stirred at room temperature for 4 hours. Water (70mL) was added at 0-5 °C and the mixture was stirred for 15 min at 0-5 °C. the solid was collected on a filter, washed with water (20 mL) and dried under vacuum (0.1 mm Hg) for 40 h 15 min to provide VI-3 (3.469 g, 151.24 mCi, 90.49% yield). Radio-TLC (CH₂ Cl₂), R_f = 0.372; HPLC (system A), RCP 99.92% (ret. time, 16.722 min).

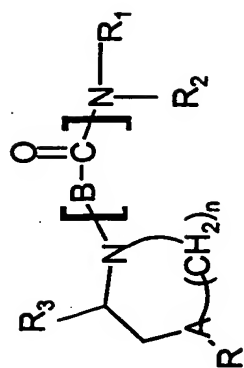
[3-¹⁴C]-3-Amino-6-trifluoromethylbenzo[b]thiophene (VI-4):

To a solution of benzo[b] thiophene (VI-3) (3.469 g, 12.6 mmol, 151.2 mCi) in NMP (14mL) was added 1-methylpiperazine (6.69g, 66.79 mmol) and the mixture was heated at 140-145 °C for 5 h. The mixture was allowed to cool to room temperature, poured into water (60mL) and extracted with ethyl acetate (140 mL). The organic extract was washed with water (30 mL), sat. sodium chloride (10mL), dried (Na₂SO₄) and the solvent was removed in *vacuo*. The residue was purified by flash chromatography on silica gel (hexane/ethyl acetate, 1/1) to yield a greenish solid which was dried under vacuum (0.1 mm HG) for 14 h to provide VI-4 (w.66g, 146.95 mCi, 97.16% yield).). Radio-TLC (hexane/ethyl acetate, 1/5), R_f = 0.407; HPLC (system A), RCP 99.44 % (ret. time, 10.552 min).

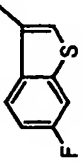
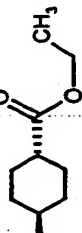
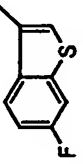
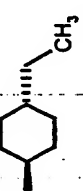
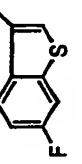
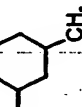
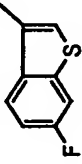

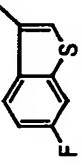

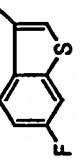

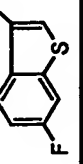

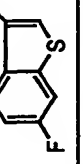
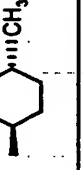
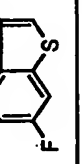
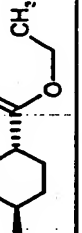
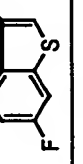

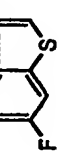
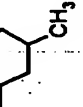
1-[6-(trifluoromethyl)benzo[b]thien-3-yl-[3-¹⁴C]piperazine (VI-5):

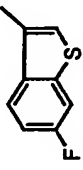


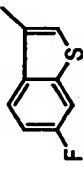


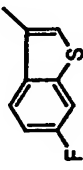


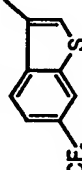

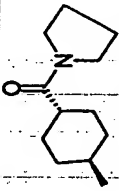
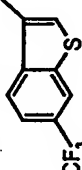

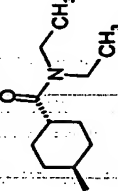
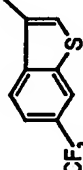

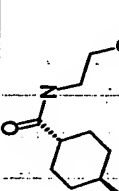
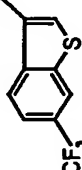
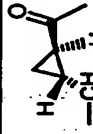
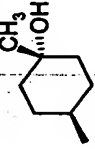
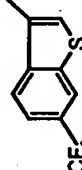

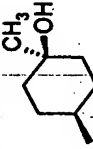



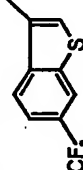


To a solution of benzo[b]thiophene (VI-4) (2.66 g, 12.24 mmol, 146.95 mCi) in NMP (17mL) was added piperazine (4.309g, 50.02 mmol) and p-toluenesulfonic acid (4.76g, 25.02 mmol) at room temperature. The mixture was heated at 170 °C for 20m h 24 min, allowed to cool to room temperature and poured into a solution of sodium carbonate (4.70 g, 44.3 mmol) in water (60mL). The mixture was extracted with ethyl acetate (20 mL), dried (Na₂SO₄) and the solvent was removed in *vacuo*. The residue was purified by flash chromatography on silica gel (CH₂Cl₂/MeOH/NH₄OH, 9/1/0.2) and product was dried under vacuum (0.1 mm Hg) for 11 h 50 min. Ethanol (absolute, 30 mL) was added to the product and solvent was removed under reduced pressure. The residue was dried under vacuum (0.1mm Hg) for 24 h 55 min to provide VI-5 (3.44 g, 144.18 mCi, 98.1% yield) as an oil. Radio-TLC (CH₂Cl₂/MeOH/NH₄OH, 9/1/0.2), R_f=0.46; HPLC (system A), RCP 99.88% (ret. time, 5.807 min).

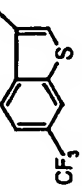

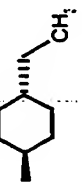
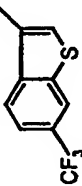

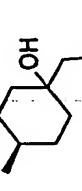
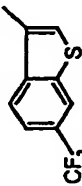

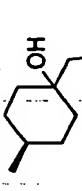
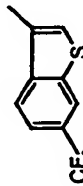

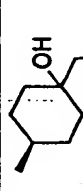
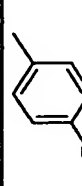

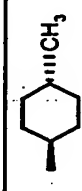
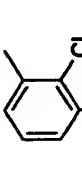

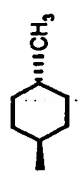
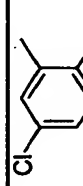

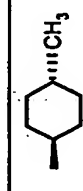
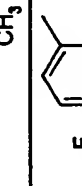

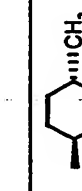
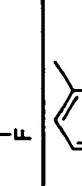
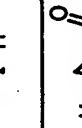
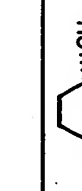
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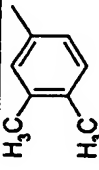

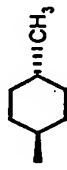
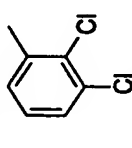
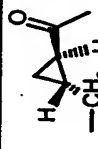
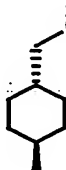
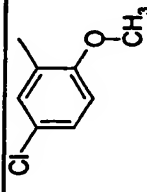

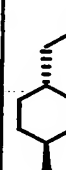
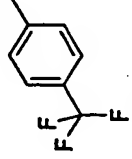
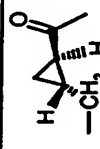
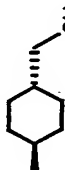
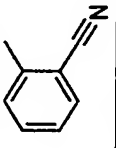

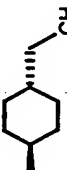
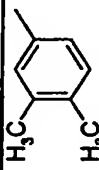

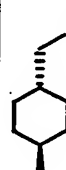
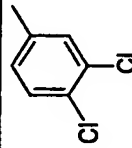


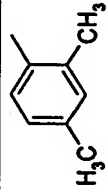


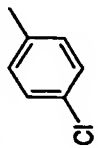
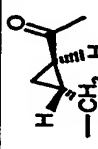
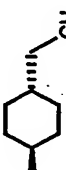


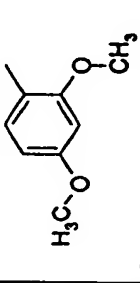
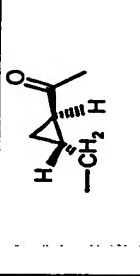
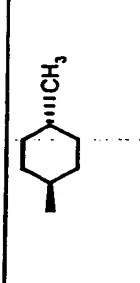
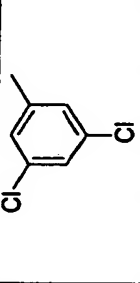
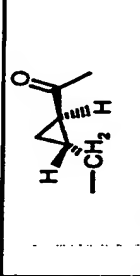
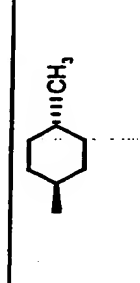
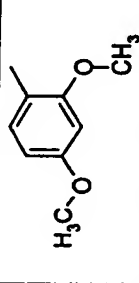
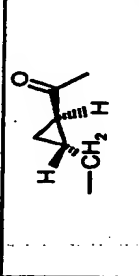
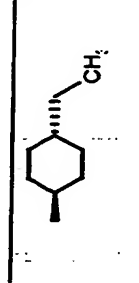
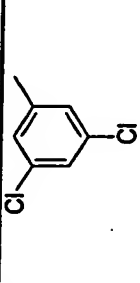
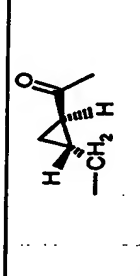
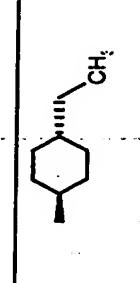
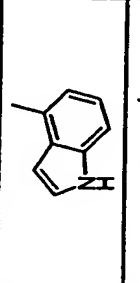
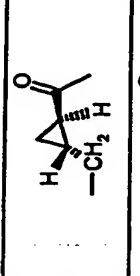
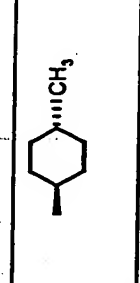
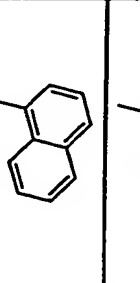
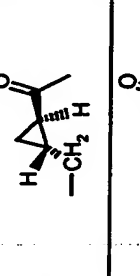
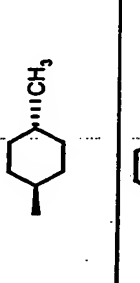
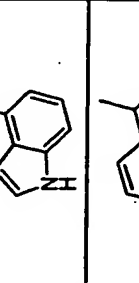
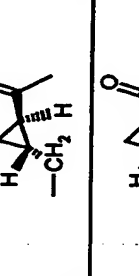
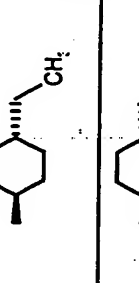
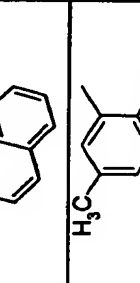
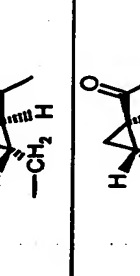
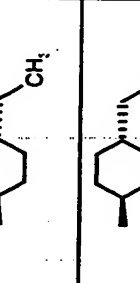
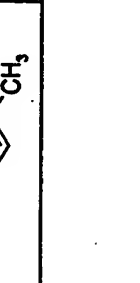
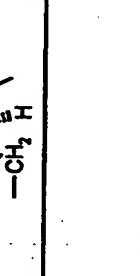
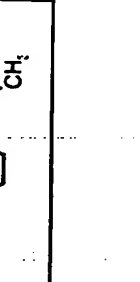
No.	R	n	$\left[\text{B}-\text{C}(=\text{O}) \right]$	R ₁	A	R ₂	R ₃	d3K _i
827055 (racemic)		2	$-(\text{CH}_2)_3-\text{C}(=\text{O})-$	H	N		CH ₂ Ph	792
827071 (racemic)		2	$-(\text{CH}_2)_3-\text{C}(=\text{O})-$	H	N		(CH ₂) ₂ Ph	454
827074 (racemic)		2	$-(\text{CH}_2)_3-\text{C}(=\text{O})-$	CH ₃	N		(CH ₂) ₂ Ph	267
827079 (racemic)		2	$-(\text{CH}_2)_3-\text{C}(=\text{O})-$	CH ₃	N		(CH ₂) ₃ Ph	126
827085 (racemic)		2	$-(\text{CH}_2)_3-\text{C}(=\text{O})-$	H	N		CH ₂ Ph	126

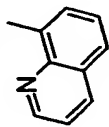
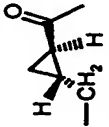
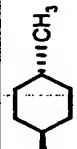
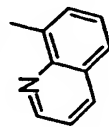
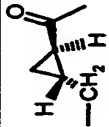

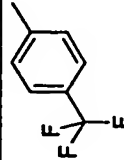
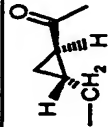

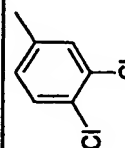
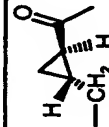
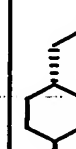
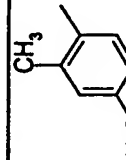
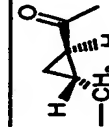
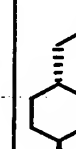
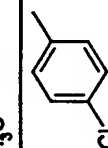
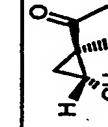
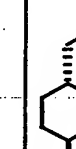
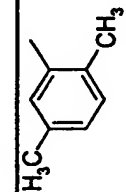
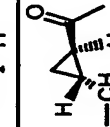
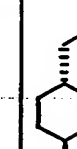
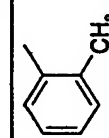
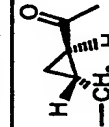
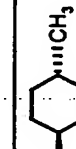
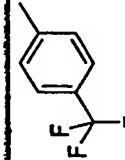
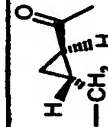
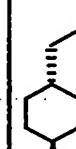
827086 (racemic)		2	$-(CH_2)_3C(=O)-$	H	N		CH ₂ Ph	334
827087 (racemic)		2	$-(CH_2)_3C(=O)-$	H	N		CH ₂ Ph	178
827088 (racemic)		2	$-(CH_2)_3C(=O)-$	H	N		CH ₂ Ph	284
827089 (racemic)		2	$-(CH_2)_3C(=O)-$	CH ₃	N		CH ₂ Ph	307
827090 (racemic)		2	$-(CH_2)_3C(=O)-$	CH ₃ CH ₂	N		CH ₂ Ph	346
827101 (racemic)		2	$-(CH_2)_3C(=O)-$	H	N		CH ₂ Ph	148
827102 (racemic)		2	$-(CH_2)_3C(=O)-$	H	N		CH ₂ Ph	218
827105 (racemic)		2	$-(CH_2)_3C(=O)-$	H	N		(CH ₂) ₃ Ph	117
827106 (racemic)		2	$-(CH_2)_3C(=O)-$	H	N		(CH ₂) ₃ Ph	317
827107 (racemic)		2	$-(CH_2)_3C(=O)-$	H	N		(CH ₂) ₃ Ph	489
827108 (racemic)		2	$-(CH_2)_3C(=O)-$	H	N		(CH ₂) ₃ Ph	302

827109 (racemic)		2		CH ₃	N		(CH ₂) ₃ Ph	78.6
827110 (racemic)		2		CH ₃ CH ₂	N		(CH ₂) ₃ Ph	208
827111 (racemic)		2		HO(CH ₂) ₂	N		(CH ₂) ₃ Ph	143
817047 (racemic)		2		H	N		H	2.86
817048 (racemic)		2		H	N		H	2.85
817049 (racemic)		2		H	N		H	7.02
817050 (-)-R ₁ R		2		H	N		H	2.15
817051 (-)-R ₁ R		2		H	N		H	3.47
817244 (racemic)		2		HO(CH ₂) ₂	N		H	
817569A (-)-R ₁ R		2		H	N		H	5.38

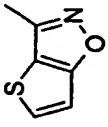

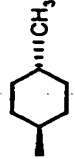
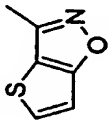

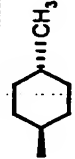
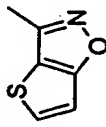
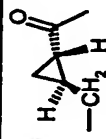

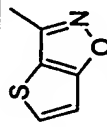


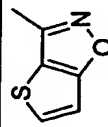
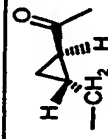
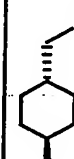
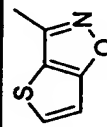
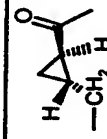
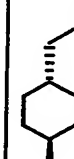
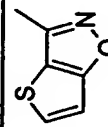
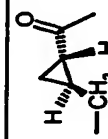
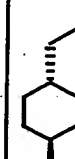
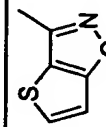
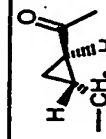
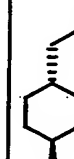
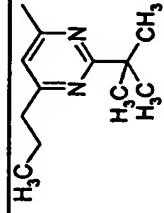
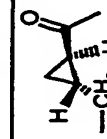
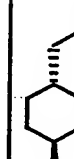
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818497 (racemic)		2		H	N		H	5.52
818673 (Isomer 1)		2		CH ₂ Ph	N		H	
818674 (Isomer 2)		2		CH ₂ Ph	N		H	
827196 (racemic)		2		H	N		H	2.35
817037 (racemic)		2		H	N		H	0.98
817038 (racemic)		2		H	N		H	0.952
817039 (racemic)		2		H	N		H	14.8
817040 (racemic)		2		H	N		H	0.804

817045 (racemic)		2		H	N		H	5.36
817041 (racemic)		2		H	N		H	0.776
817042 (racemic)		2		H	N		H	0.615
817043 (racemic)		2		H	N		H	7.2
817044 (racemic)		2		H	N		H	1.1
817046 (racemic)		2		H	N		H	1.92
817090 (-)-R,R		2		H	N		H	2.17
817091 (-)-R,R		2		H	N		H	3.98
817092 (-)-R,R		2		H	N		H	3.39


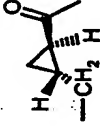


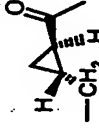

817094		2		H	N		H	8.89
817095		2		H	N		H	0.671
817096		2		H	N		H	9.09
817097		2		H	N		H	0.636
817098		2		H	N		H	1.06
817099		2		H	N		H	1.1
817100		2		H	N		H	0.75
817101		2		H	N		H	0.547
817102 (-)-R,R		2		H	N		H	7.75

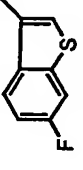

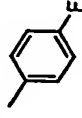
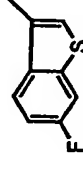

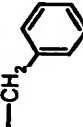
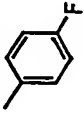
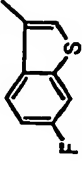

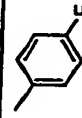
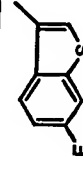

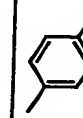
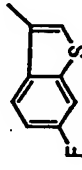
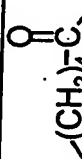

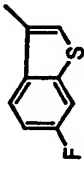

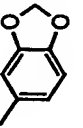
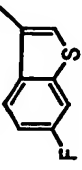

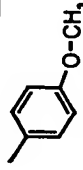
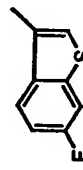
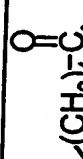
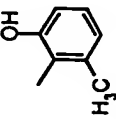
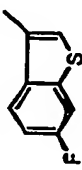

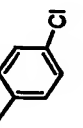
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817090A (racemic)		2		H	N		H	5.04
817571A (racemic)		2		H	N		H	11.5
817092A (racemic)		2		H	N		H	22.3
817570A (racemic)		2		H	N		H	5.04
817478A (racemic)		2		H	N		H	1.99
817043A (racemic)		2		H	N		H	18.6

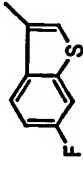
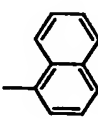
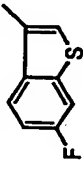
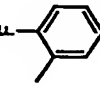
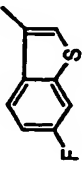
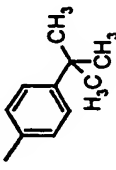
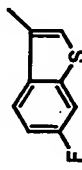
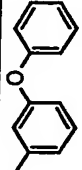
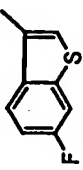
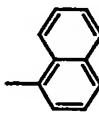
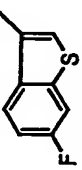


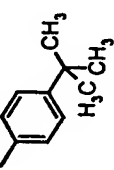
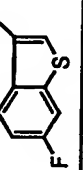
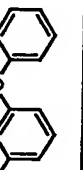

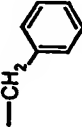
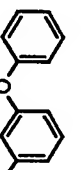
817091A (-)-R,R		2		H	N		H	4.04
817102A (-)-R,R		2		H	N		H	7.57
818675DA (-)-R,R		2		H	N		H	5.69
827201 (racemic)		2		H	N		H	126
817093 (-)-R,R		2		H	N		H	5.97
817480A (racemic)		2		H	N		H	5.33
817566		2		H	N		H	2.46
817565		2		H	N		H	1.73
827198		2		H	N		H	161

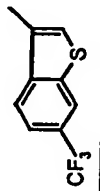

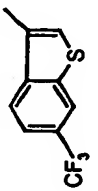
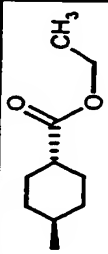
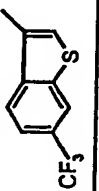
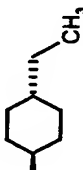
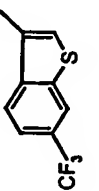
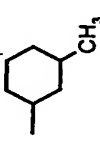
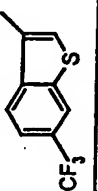
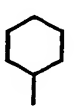
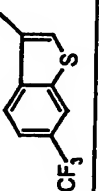
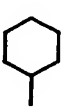
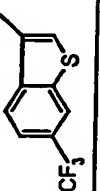
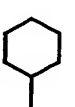
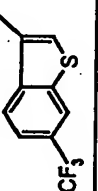
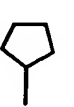
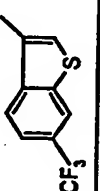
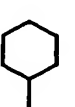
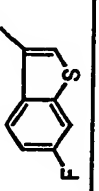

818427 (racemic)		2		H	N		H	6.07
817892 (-)-R,R		2		H	N		H	5.47
817893 (+)-S,S		2		H	N		H	245
817892A (-)-R,R		2		H	N		H	3.02
818574 (racemic)		2		H	N		H	9.6
817787 (-)-R,R		2		H	N		H	5.81
817786 (+)-S,S		2		H	N		H	125
817787A (-)-R,R		2		H	N		H	1.76
817272 (racemic)		3		H	N		H	1.72

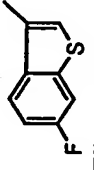
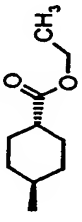
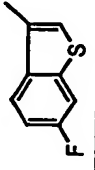
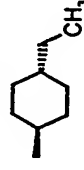
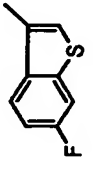
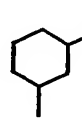
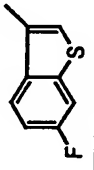

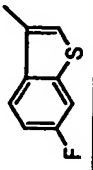

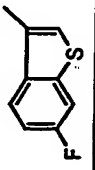

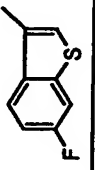

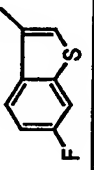

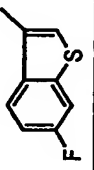
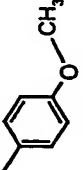
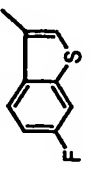
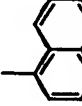
817273 (racemic)		3		H	N		H	3.05
817260 (racemic)		3		H	N		H	12.5
817261 (racemic)		3		H	N		H	9.23
827731 (racemic)		3		H	N		H	19.5
827732 (racemic)		3		H	N		H	10.5
817567 (racemic)		3		H	N		H	80.6
817568 (racemic)		3		H	N		H	36.3
827733 (racemic)		3		H	N		H	1.19

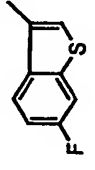
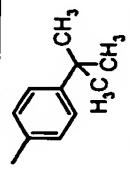
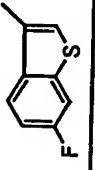
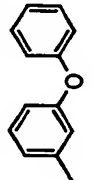
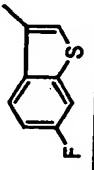
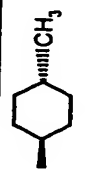
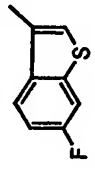
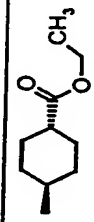
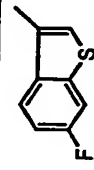
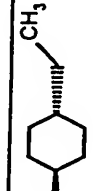
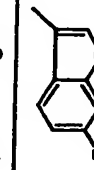
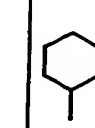
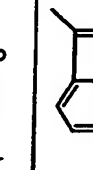
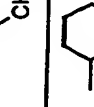
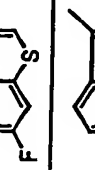
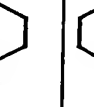
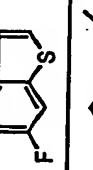
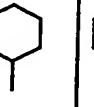
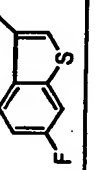
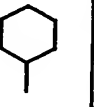
818498 (racemic)		3		H	N		H	25.6
827800 (racemic)		3		H	N		H	19.7

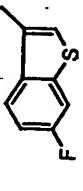
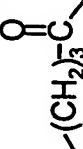

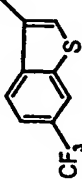


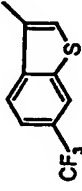


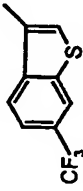
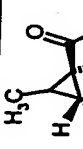

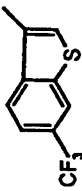
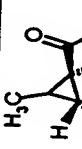
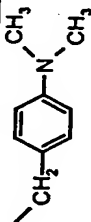
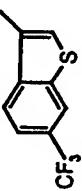


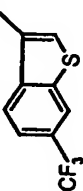

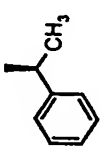
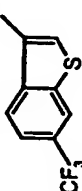

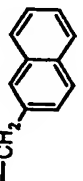
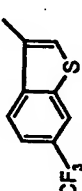


814648		2		$\text{CH}_3(\text{CH}_2)_2$	N		H	39.6
814649		2			N		H	38.9
814650A		2		CH_3	N		H	18
813384		2		H	N		H	74
822129		2		CH_3	N		H	38
822130		2		CH_3CH_2	N		H	51
822131		2		CH_3	N		H	61
822132		2		CH_3CH_2	N		H	18
822133		2		CH_3	N		H	17

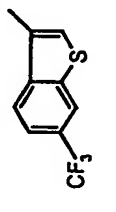
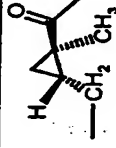
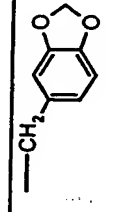
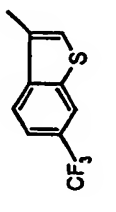
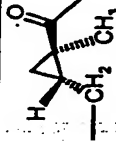
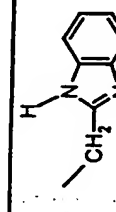
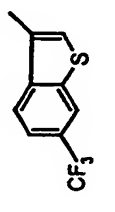
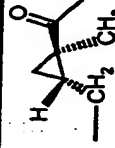
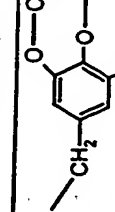
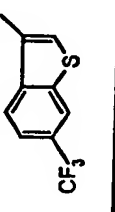
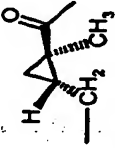
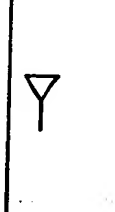
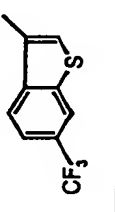
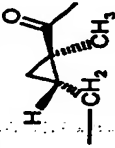
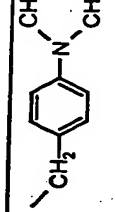
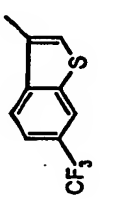
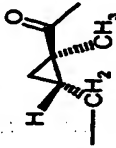
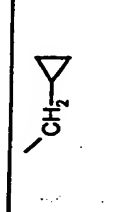
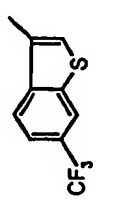
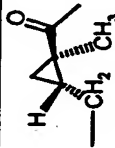
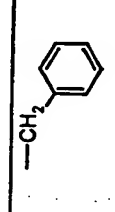
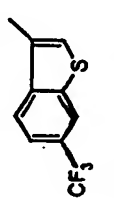
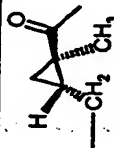
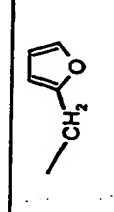
822134		2	$-(CH_2)_4-C(=O)-$	H	N		H	82
822135		2	$-(CH_2)_4-C(=O)-$	H	N		H	3.6
822136		2	$-(CH_2)_4-C(=O)-$	H	N		H	207
822137		2	$-(CH_2)_4-C(=O)-$	H	N		H	36
822138		2	$-(CH_2)_4-C(=O)-$	CH ₃	N		H	81
822139		2	$-(CH_2)_4-C(=O)-$	CH ₃	N		H	21.2
822140		2	$-(CH_2)_4-C(=O)-$	CH ₃	N		H	112.8
822142		2	$-(CH_2)_4-C(=O)-$	CH ₃	N		H	39.1
822143		2	$-(CH_2)_4-C(=O)-$		N		H	338

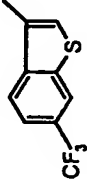

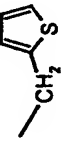
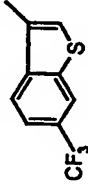
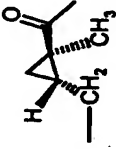

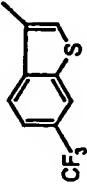
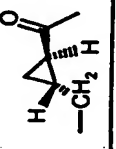
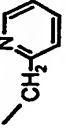
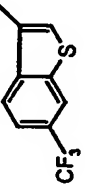
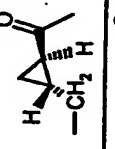

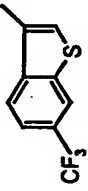
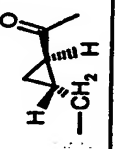
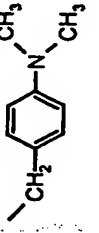
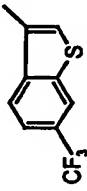
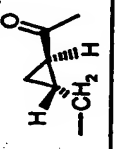
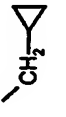
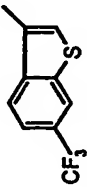
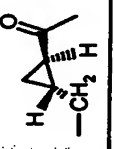
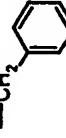
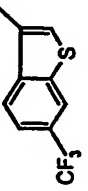
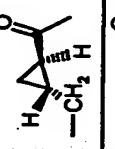
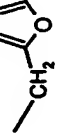
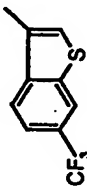
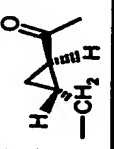
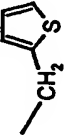
826804		2	$-(CH_2)_3-C(=O)-$	H	N		H	67.4
826805		2	$-(CH_2)_3-C(=O)-$	H	N		H	14.2
826806		2	$-(CH_2)_3-C(=O)-$	H	N		H	40
826807 (racemic)		2	$-(CH_2)_3-C(=O)-$	H	N		H	43
826808		2	$-(CH_2)_3-C(=O)-$	CH ₃	N		H	17.4
826809		2	$-(CH_2)_3-C(=O)-$	CH ₃ CH ₂	N		H	71
826810		2	$-(CH_2)_3-C(=O)-$	HO(CH ₂) ₂	N		H	86.7
826820		2	$-(CH_2)_3-C(=O)-$	H	N		H	52.8
826821		2	$-(CH_2)_3-C(=O)-$	H	N		H	70.1
826824		3	$-(CH_2)_3-C(=O)-$	H	N		H	34.2

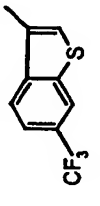

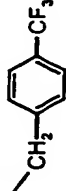
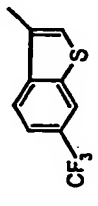
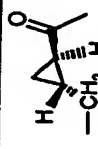

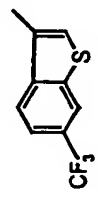


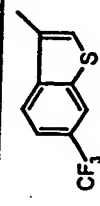


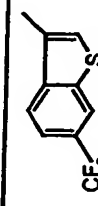

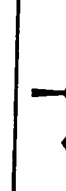
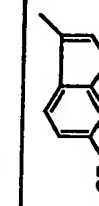

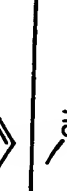
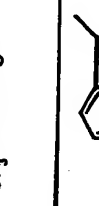
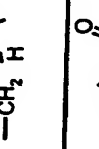
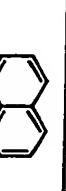
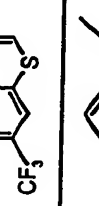

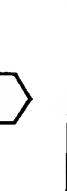
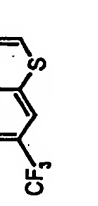

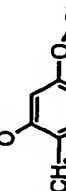
826825		3	$-(CH_2)_3-C(=O)-$	H	N		H	74.9
826826		3	$-(CH_2)_3-C(=O)-$	H	N		H	27.4
826827 (racemic)		3	$-(CH_2)_3-C(=O)-$	H	N		H	39.5
826828		3	$-(CH_2)_3-C(=O)-$	CH ₃	N		H	14.4
826829		3	$-(CH_2)_3-C(=O)-$	CH ₃ CH ₂	N		H	15
826830		3	$-(CH_2)_3-C(=O)-$	HO(CH ₂) ₂	N		H	25.1
826840		3	$-(CH_2)_3-C(=O)-$	H	N		H	11
826841		3	$-(CH_2)_3-C(=O)-$	H	N		H	22
822144		2	$-(CH_2)_3-C(=O)-$	CH ₃	N		H	144
822145		2	$-(CH_2)_3-C(=O)-$	H	N		H	176

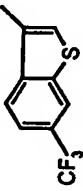

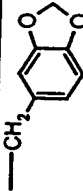
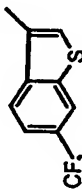

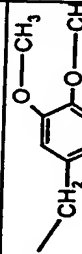
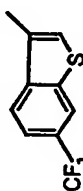

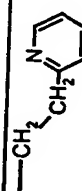
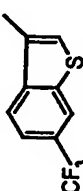


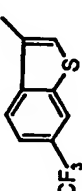


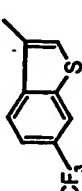


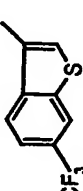


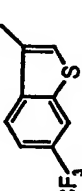


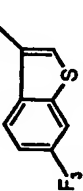


822147		2	$-(CH_2)_3-C(=O)-$	H	N		H	217
822148		2	$-(CH_2)_3-C(=O)-$	H	N		H	41.4
826844		2	$-(CH_2)_3-C(=O)-$	H	N		H	0.591
826845		2	$-(CH_2)_3-C(=O)-$	H	N		H	4.42
826846		2	$-(CH_2)_3-C(=O)-$	H	N		H	17.6
826847		2	$-(CH_2)_3-C(=O)-$	H	N		H	1.01
826848		2	$-(CH_2)_3-C(=O)-$	CH ₃	N		H	4.35
826849		2	$-(CH_2)_3-C(=O)-$	CH ₃ CH ₂	N		H	54.2
826850		2	$-(CH_2)_3-C(=O)-$	HO(CH ₂) ₂	N		H	18.8
826860		2	$-(CH_2)_3-C(=O)-$	H	N		H	3.48

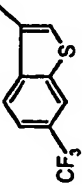
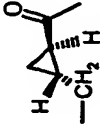
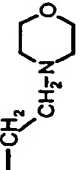
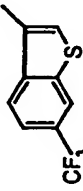
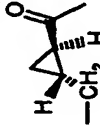

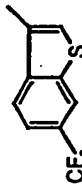

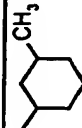
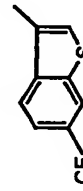


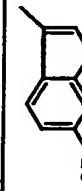



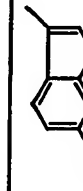

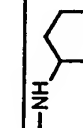
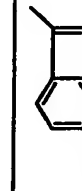


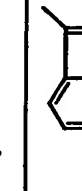
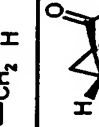

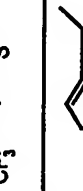
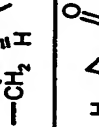

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825870 Racemic		2		H	N		H	100
825871 Racemic		2		H	N		H	137
825872 Racemic		2		H	N		H	104
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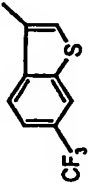

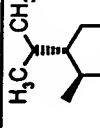
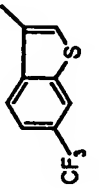

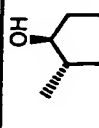
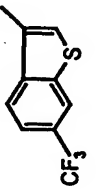
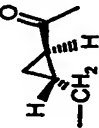
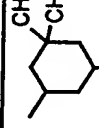
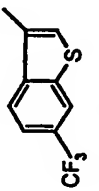

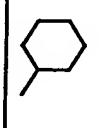
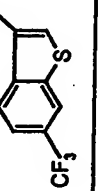

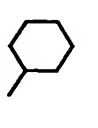
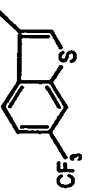
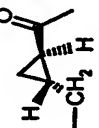
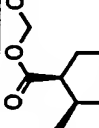
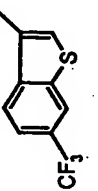
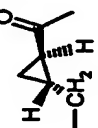
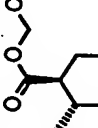
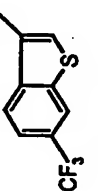
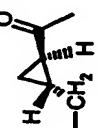
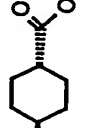
825886		2		H	N		H	40.2
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825894		2		H	N		H	59
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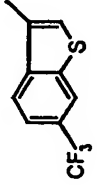
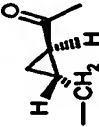

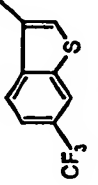
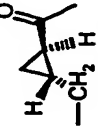

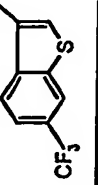
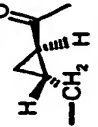

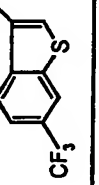
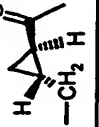

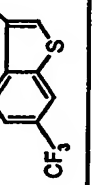

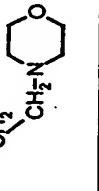
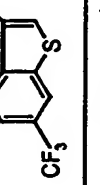


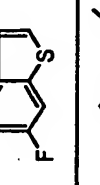
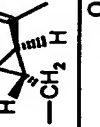
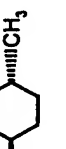
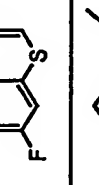
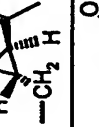
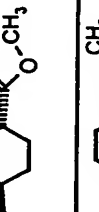
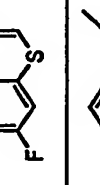


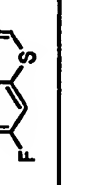

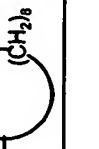
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822202		2		H	N		H	8.1
826066		2		H	N		H	60.3
826067		2		H	N		H	19.3
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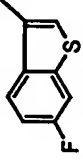


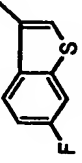


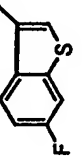

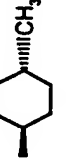
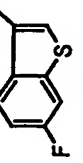

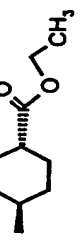
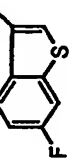


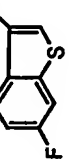

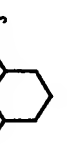
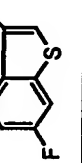


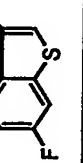


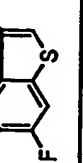


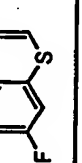


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826074		2		H	N		H	72.6
826075		2		H	N		H	55.6
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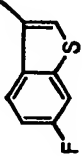


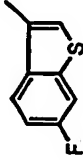

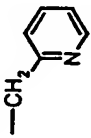
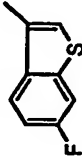

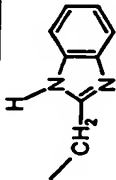
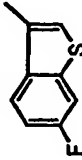


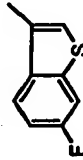

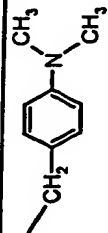
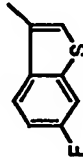


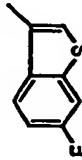

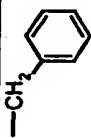
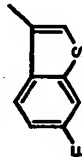

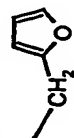
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(+)-816589 (S,S)		2		H	N		H	1070
(-)-817569 (R,R)		2		H	N		H	2.62
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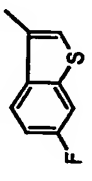
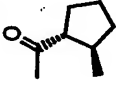
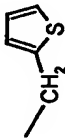
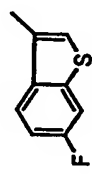
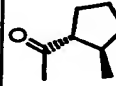
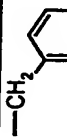
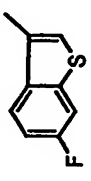
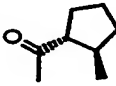
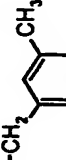
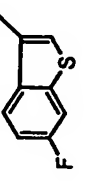
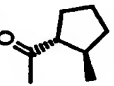

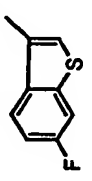
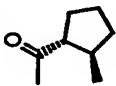

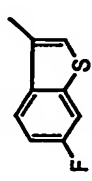
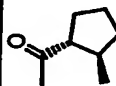
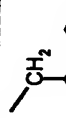
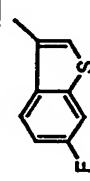
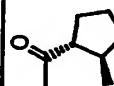


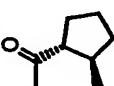
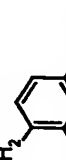
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826886		2			N		H	136
826887		2		H	N		H	83.8
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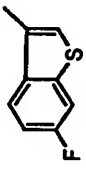
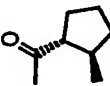
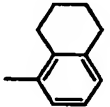
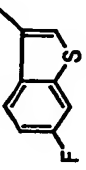
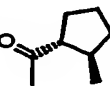
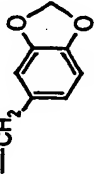
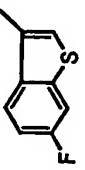
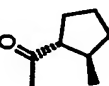

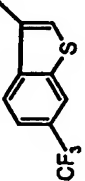
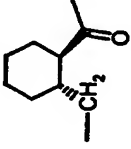
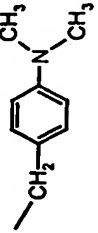
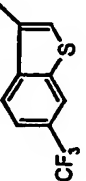
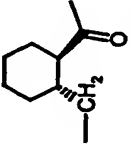
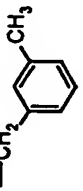
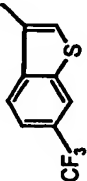
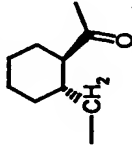
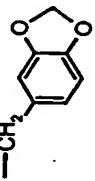
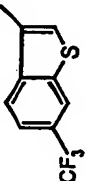
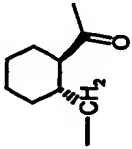

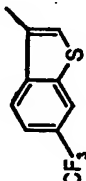
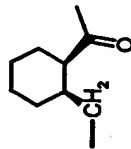
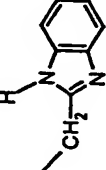
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826893		2		H	N		H	20.4
826894		2		CH ₃ CH ₂	N		H	35
826895		2		HO(CH ₂) ₂	N		H	48.8
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816078A HCl salt		2		H	N		H	89.7

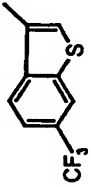
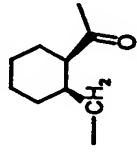
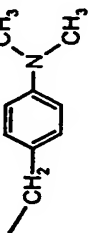
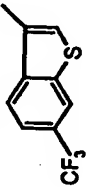
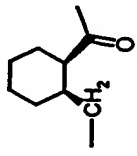

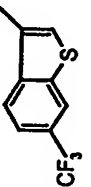
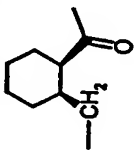
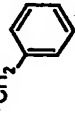
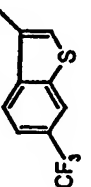
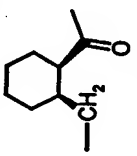
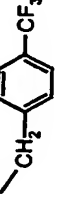
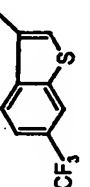
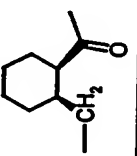

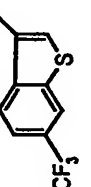
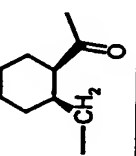
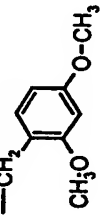
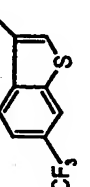
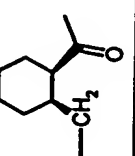
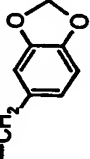
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8266682		3		H	N		H	103
8266684		3		H	N		H	7.9
8266665		2		H	N		H	1.9
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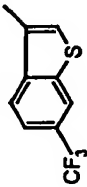
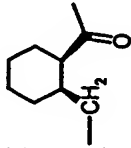
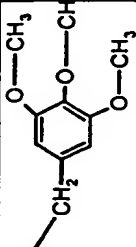
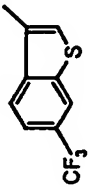
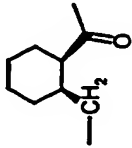
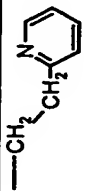
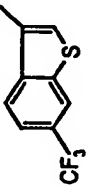
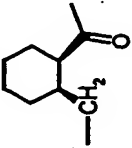

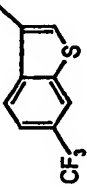
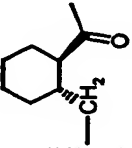
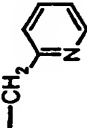
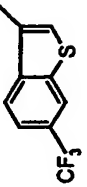
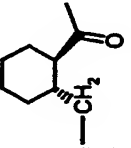

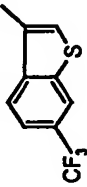
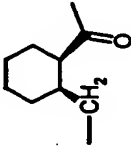
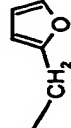
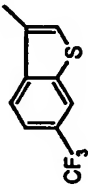
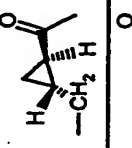
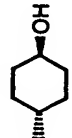
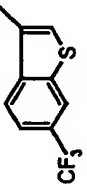
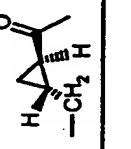
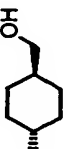
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826864		3		H	N		H	2.16
826865		3		H	N		H	3.68
826866		3		H	N		H	1.24
826867		3		H	N		H	1.89
826868		3		CH ₃	N		H	3.49
826869		3		CH ₃ CH ₂	N		H	6.75
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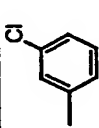

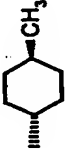
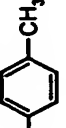

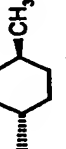
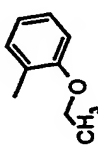
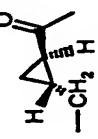
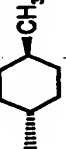
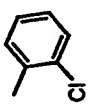
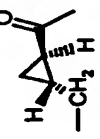
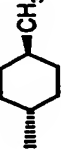
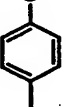
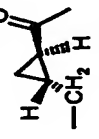
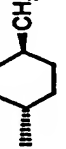
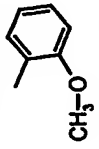

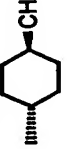
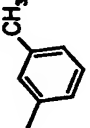

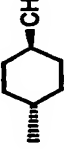
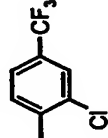

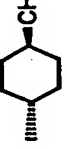
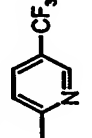

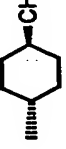
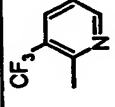

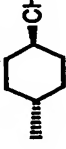
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825825		2		H	N		H	152
825826G (Maleate Salt)		2		H	N		H	32.5
825827		2		H	N		H	54.8
825828		2		H	N		H	21.8
825829G (Maleate Salt)		2		H	N		H	40.1
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825831		2		H	N		H	48.1

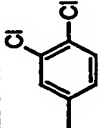

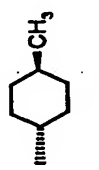
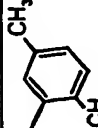

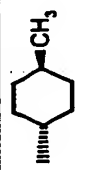
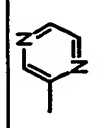
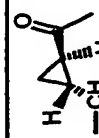
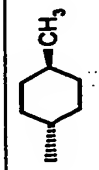
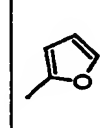

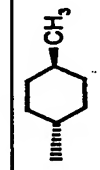
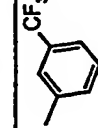

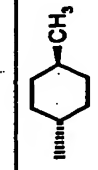
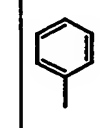
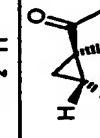
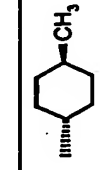
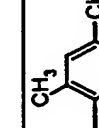
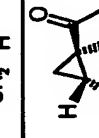
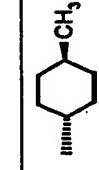
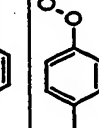

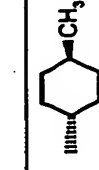
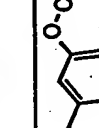
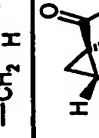
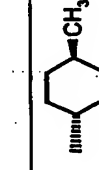
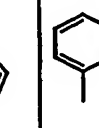
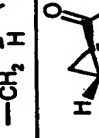
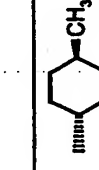
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825900		2		H	N		H	22.4
826057		2		H	N		H	90.9
826058		2		H	N		H	45.2
826059		2		H	N		H	27.1
826060		2		H	N		H	40.2
826061		2		H	N		H	




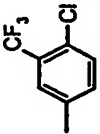

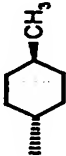
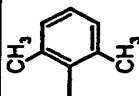

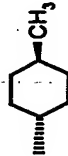
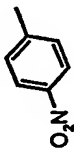


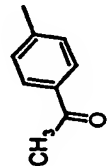

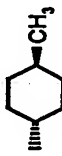
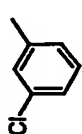

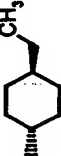
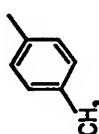

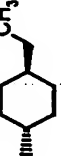
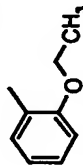

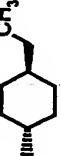


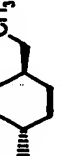
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826063		2		H	N		H	
826064		2		H	N		H	
826086		2		H	N		H	103
826092		2		H	N		H	293
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826100		2		H	N		H	193
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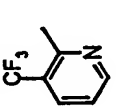
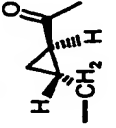
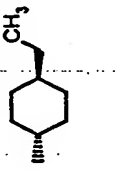
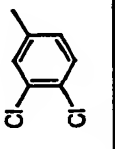
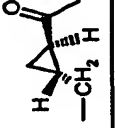
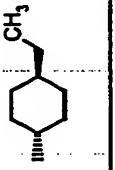
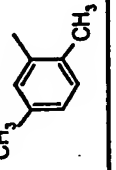
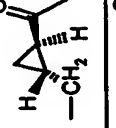
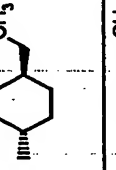

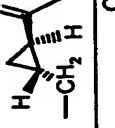
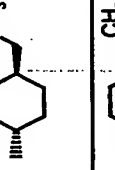
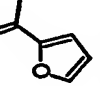
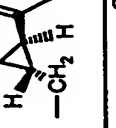
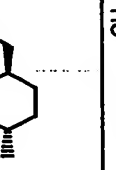
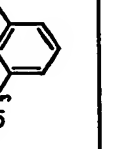
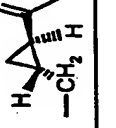
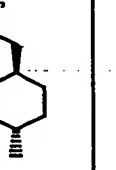
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

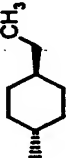
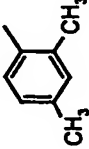

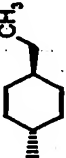
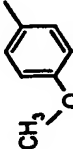

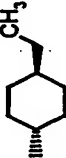
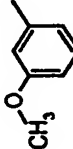

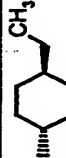
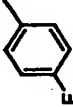

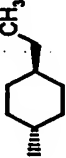
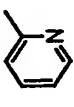

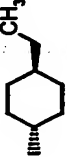
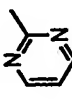

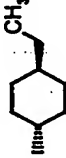
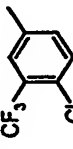

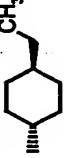
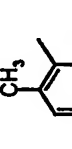

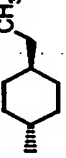
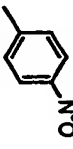

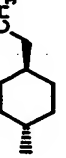
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826121		2		H	N		H	502
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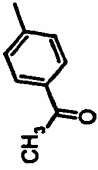
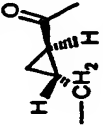
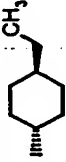
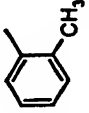

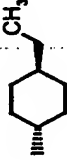
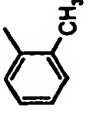

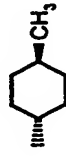
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827176		2		H	N		H	1.18
827177		2		H	N		H	1
827178		2		H	N		H	12.4
827179		2		H	N		H	1.04
827180		2		H	N		H	2.47
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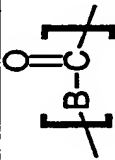
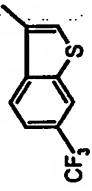

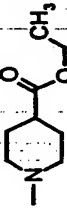
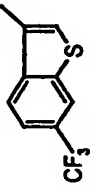
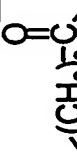
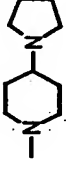
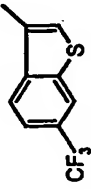

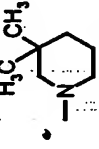
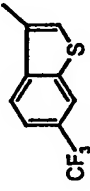

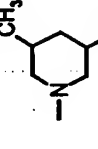
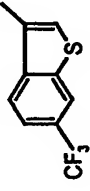
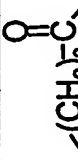
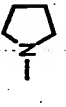
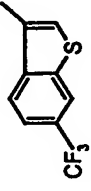
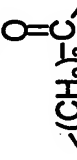
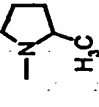
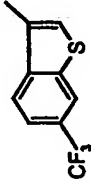

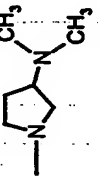
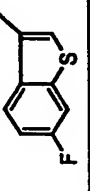
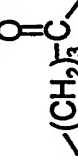
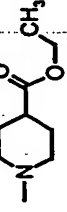
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827187		2		H	N		H	10.6
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827190		2		H	N		H	2.42
827191		2		H	N		H	0.724
827193		2		H	N		H	40.6
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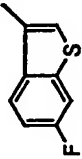

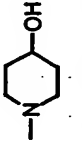
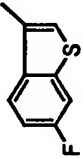

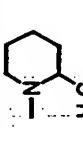
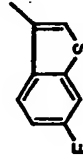

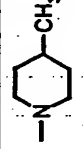
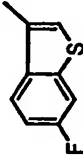

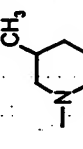
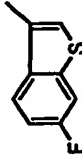

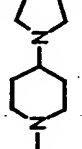
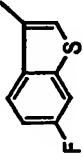

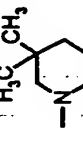
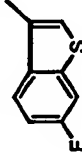

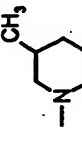
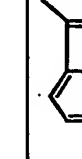

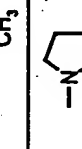
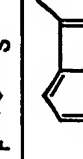


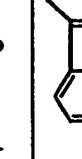
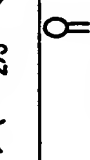
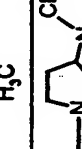
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827206		2		H	N		H	59.7
827212		2		H	N		H	1.2
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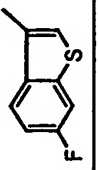

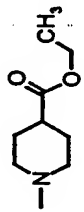
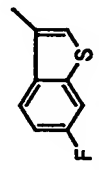

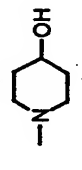
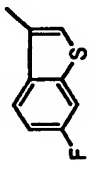

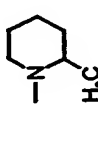
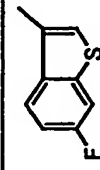

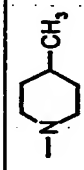
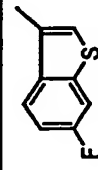

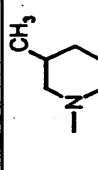
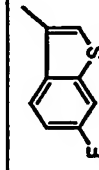

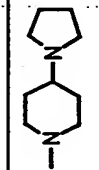
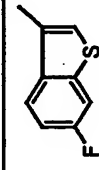

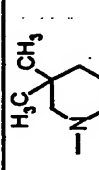
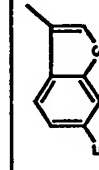

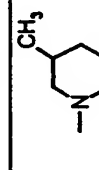
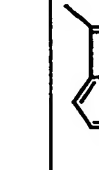

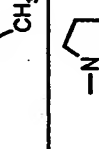
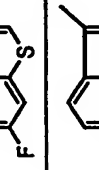

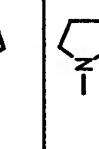
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828393		2		H	N		H	3.45
817570 (Racemic)		2		H	N		H	6.24
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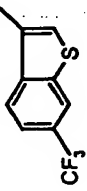
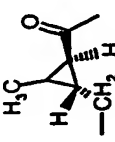
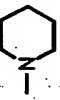
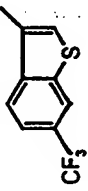
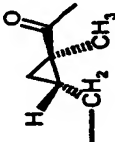

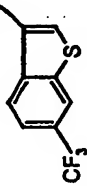
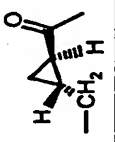

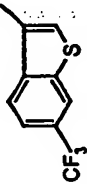
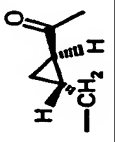

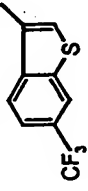
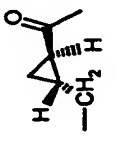
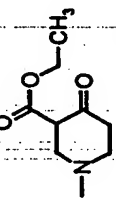
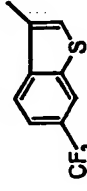
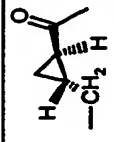
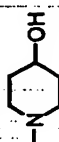
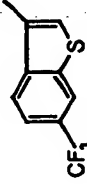
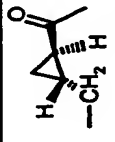
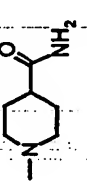
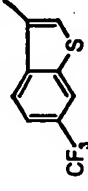
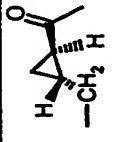
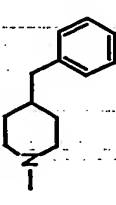
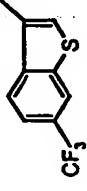
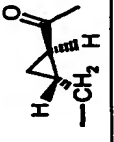
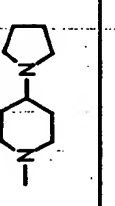
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827233		2		H	N		H	27.7
827234		2		H	N		H	3.15
827235		2		H	N		H	4.49
827214		2		H	N		H	6.13
827236		2		H	N		H	12.9
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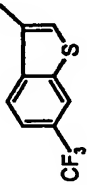

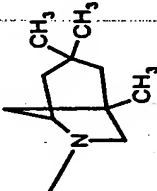
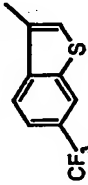

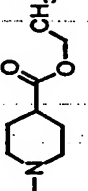
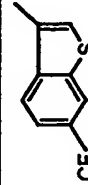
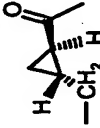
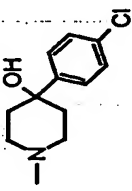
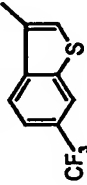


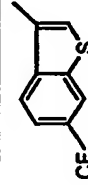

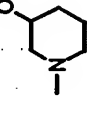
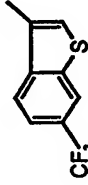

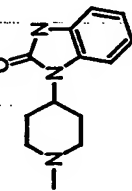
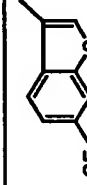
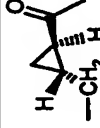
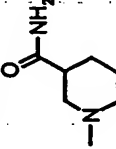
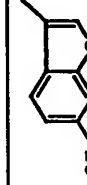

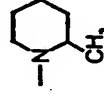
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817478 (Racemic)		2		H	N		H	1.46

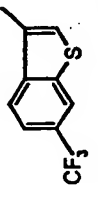
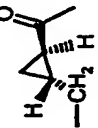
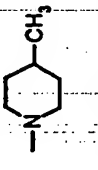
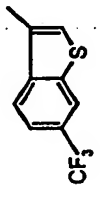

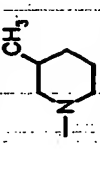
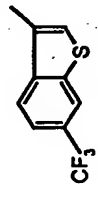

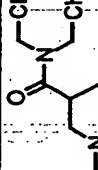
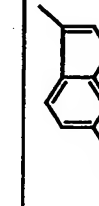

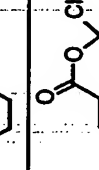
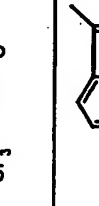
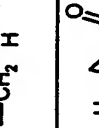
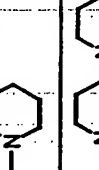
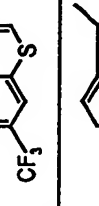

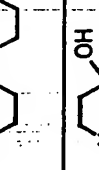
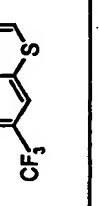
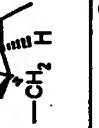
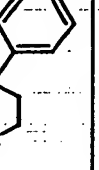
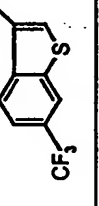
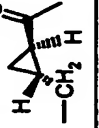
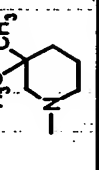
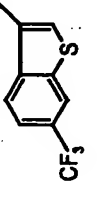

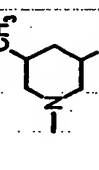
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826816		2		N		H	26.3
826817		2		N		H	20
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826819		2		N		H	11.6
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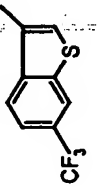

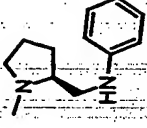
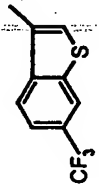

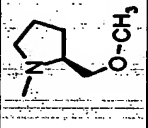
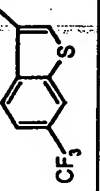
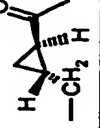
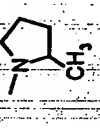
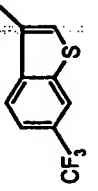

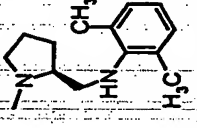
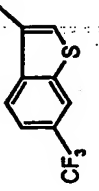

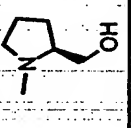
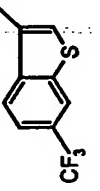

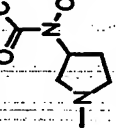
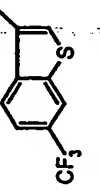

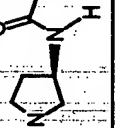
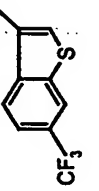

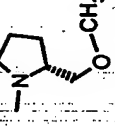
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826836		3		N		H	2.23
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826838		3		N		H	14.6
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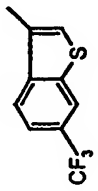

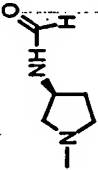
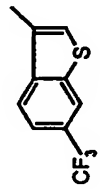

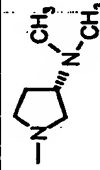
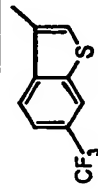
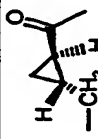
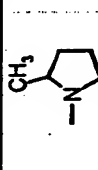
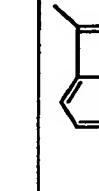

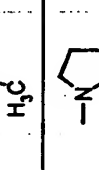
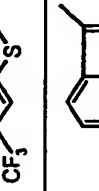
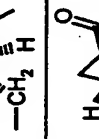
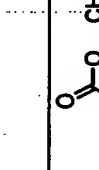
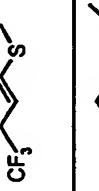
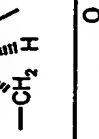
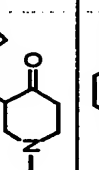
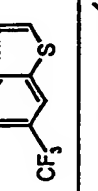
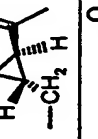
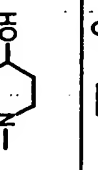
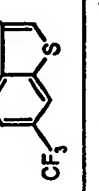
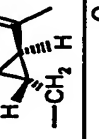
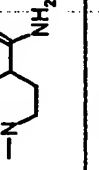
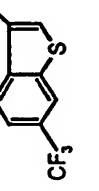
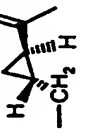
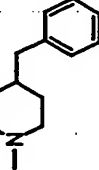
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826856		2		N		H	1.8
826857		2		N		H	0.817
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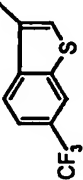


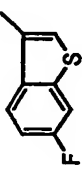


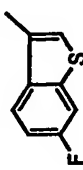

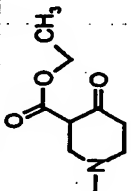
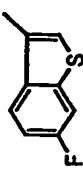
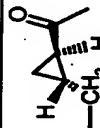

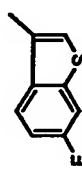
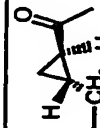
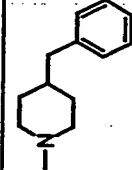
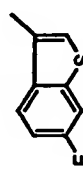

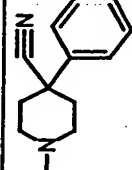
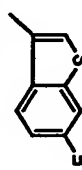

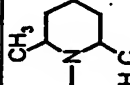
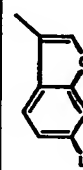


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826659		2		N		H	140
826660		2		N		H	53
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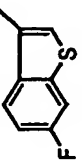
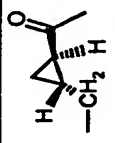
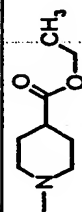
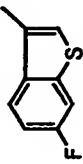
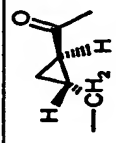
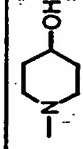
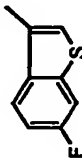
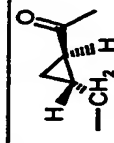
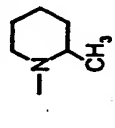
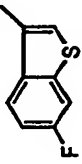
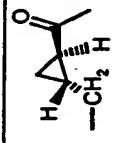
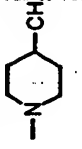
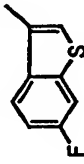
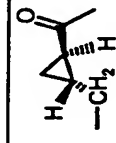
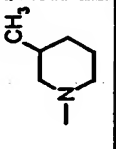
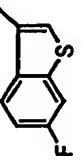

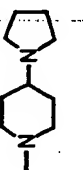
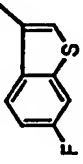
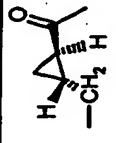
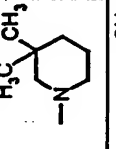
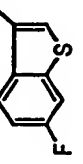
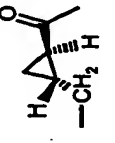
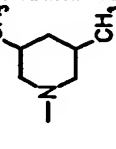
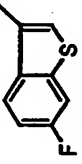
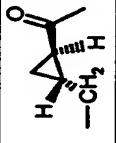
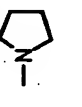
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826902		2		N		H	13.1
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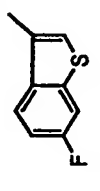

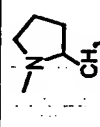
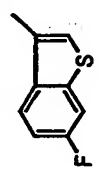

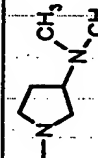
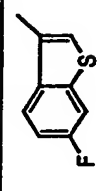
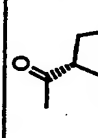
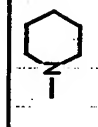
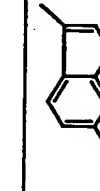
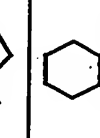
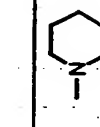
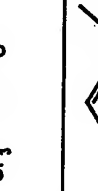
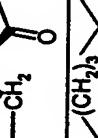

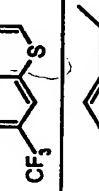
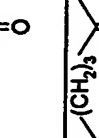
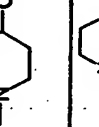
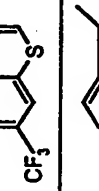
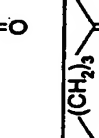
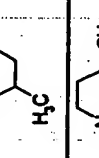
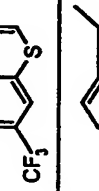
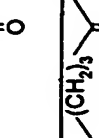
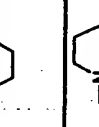
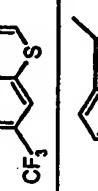
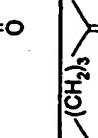
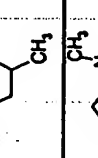
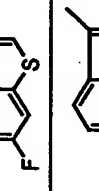
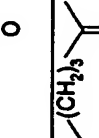
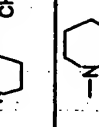
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826910		2		N		H	17.5
826911		2		N		H	93
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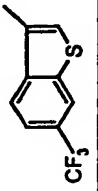
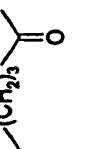
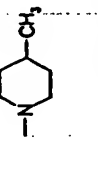
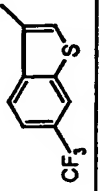
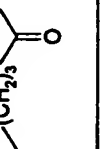
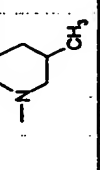
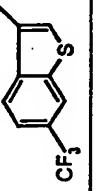
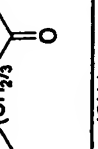
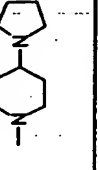
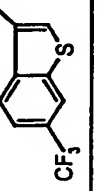
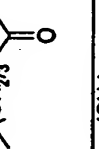
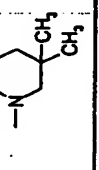
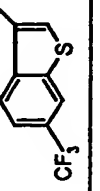
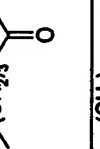
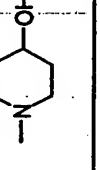
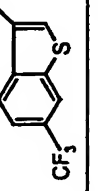
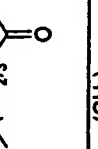
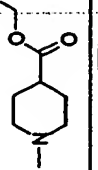
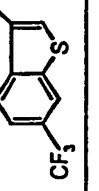
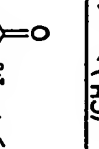
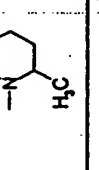
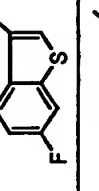
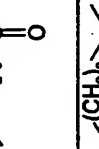
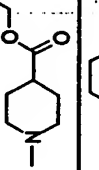
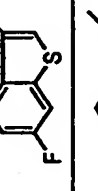
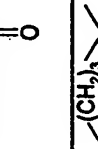
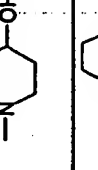
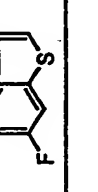
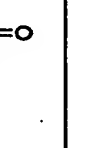
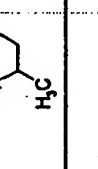
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826920		2		N		H	67.6
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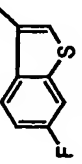
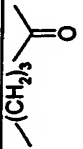
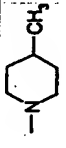
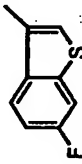
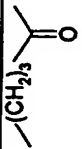
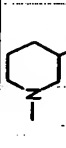
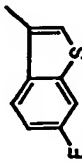
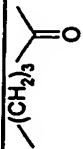
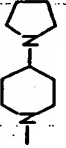
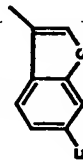
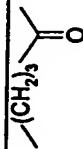
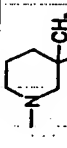
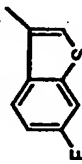
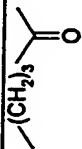
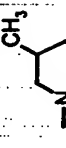
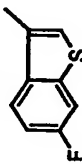


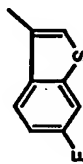
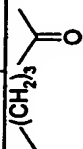
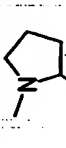
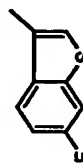
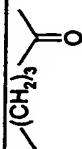
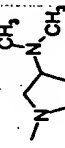
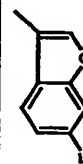
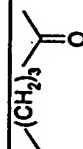
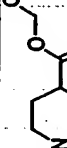
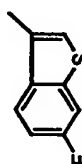
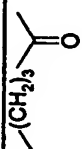
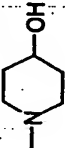
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826685		3		N		H	154
826686		3		N		H	26
826687		3		N		H	132
826688		3		N		H	217
826689		3		N		H	674

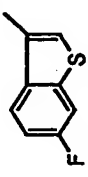
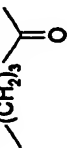
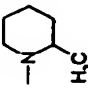
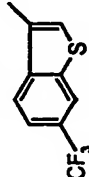

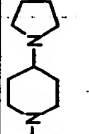
8266691		3		N		H	35
8266669		2		N		H	0.24
8266671		2		N		H	6.8
8266672		2		N		H	0.64
8266673		2		N		H	7.9
8266674		2		N		H	48
8266675		2		N		H	8
8266676		2		N		H	2

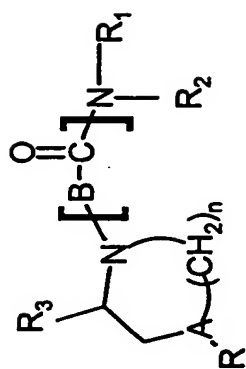
826871		3		N		H	10.7
826872		3		N		H	3.66
826873		3		N		H	1.31
826874		3		N		H	1.72
826875		3		N		H	2.79
826876		3		N		H	2.72
826877		3		N		H	4.72
826878		3		N		H	7.95
826879		3		N		H	1.59

826882		3		N		H	2.93
826883		3		N		H	13.4
826056		2		N		H	5.4
826119		2		N		H	219
826812		2		N		H	7.29
826813		2		N		H	5.16
826814		2		N		H	10.3
826815		2		N		H	31.7
826863		2		N		H	26.6
827064		2		N		PhCH ₂	245

827065		2		N		PhCH ₂	168
827066		2		N		PhCH ₂	209
827067		2		N		PhCH ₂	268
827068		2		N		PhCH ₂	197
827063		2		N		PhCH ₂	373
827082		2		N		Ph(CH ₂) ₃	303
827084		2		N		Ph(CH ₂) ₃	266
827092		2		N		PhCH ₂	316
827093		2		N		PhCH ₂	84
827094		2		N		PhCH ₂	34.6

827095		2		N		PhCH ₂	37.8
827096		2		N		PhCH ₂	44.7
827097		2		N		PhCH ₂	51.5
827098		2		N		PhCH ₂	82.9
827099		2		N		PhCH ₂	144
827100		2		N		PhCH ₂	63.5
827103		2		N		PhCH ₂	81.7
827104		2		N		PhCH ₂	141
827112		2		N		Ph(CH ₂) ₃	126
827113		2		N		Ph(CH ₂) ₃	95

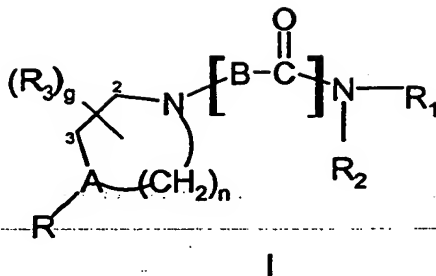
827114		2		N		Ph(CH ₂) ₃	120
826690 (racemic)		3		N		H	83% Inh @ 0.1 nM



No.	R	n	$\left[\text{B}-\text{C} \right]$	R ₁	A	R ₂	R ₃	d3K _i
817274		2		H	N		H	4.49
817275		2		H	N		H	3.34

We claim:

1. A compound of the formula (I):



I

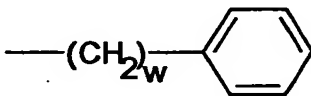
wherein

A is CH or N;

n is 2 or 3;

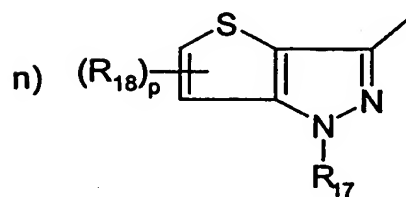
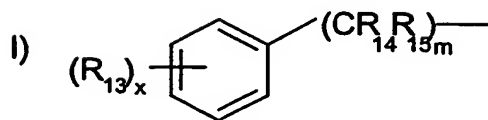
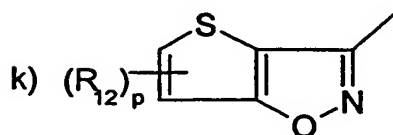
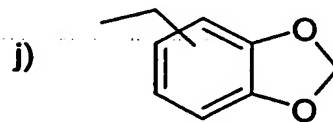
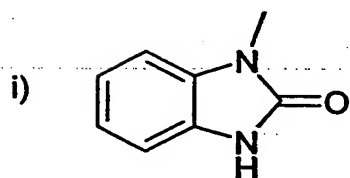
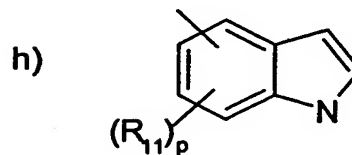
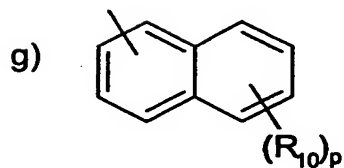
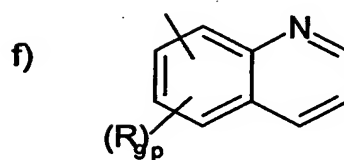
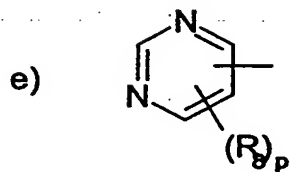
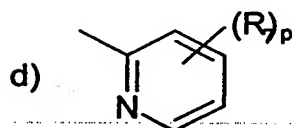
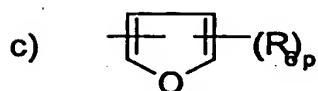
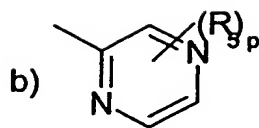
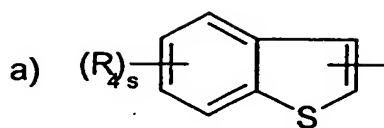
g is 1 or 2;

each R₃ is independently hydrogen, C₁-C₆alkyl, or



wherein w is 1, 2, or 3;

R is selected from the group consisting of (a) - (n):



wherein

5 each $R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}$ and R_{18} is independently hydrogen, C_1 - C_6 alkyl, halogen, trifluoromethyl or $-CH_2OC_1$ - C_6 alkyl; p, s and x are 0, 1, or 2;

each R_{13} is independently hydrogen, C_1 - C_6 alkyl, halogen, trifluoromethyl, C_1 - C_6 alkoxy, nitro, CN, or COC_1 - C_6 alkyl;

10 R_{16} is C_1 - C_6 alkyl;

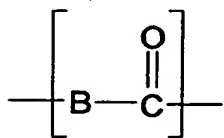
each R_{14} and R_{15} is independently hydrogen or C_1 - C_6 alkyl;

R_{17} is hydrogen, C_1 - C_6 alkyl, Ar, $-COAr$, $-CONHAr$ or $-SO_2$ -Ar wherein

Ar is a phenyl group which is unsubstituted or mono- or di-substituted with substituents independently selected from C_1 - C_6 alkyl, halogen, trifluoromethyl, C_1 - C_6 alkoxy, nitro, CN and COC_1 - C_6 alkyl; and

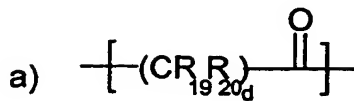
15

m is 0, 1, or 2;



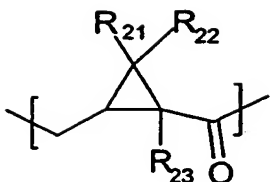
represents a group selected from (a) - (e):

20



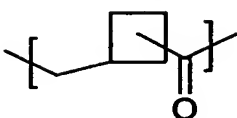
25

b)

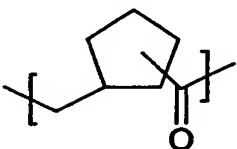


5

(c)

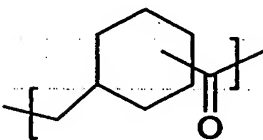


(d)



10

(e)



15

wherein

each R_{19} and R_{20} is independently hydrogen, hydroxy or C_1 - C_6 alkyl;

R_{21} , R_{22} , and R_{23} are each independently hydrogen or C_1 - C_3 linear alkyl; and

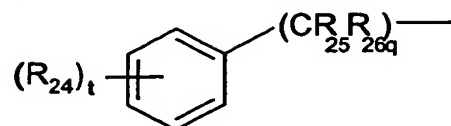
20

d is 3 or 4;

R_1 is a) hydrogen;

b) C₁-C₆alkyl, unsubstituted or mono- or di-substituted with hydroxy; or

c)



5

wherein

each R₂₄ is independently hydrogen or C₁-C₆alkyl;

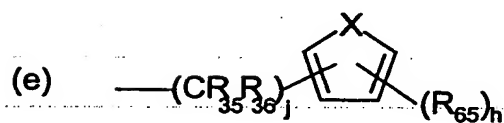
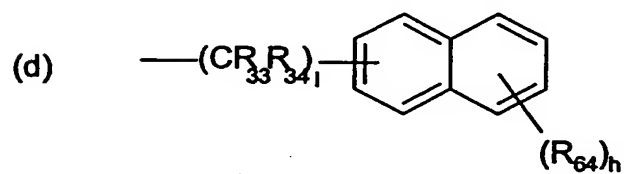
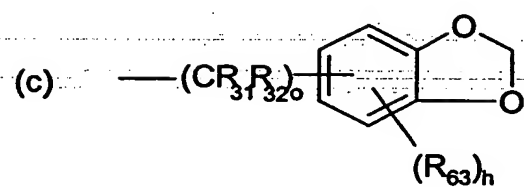
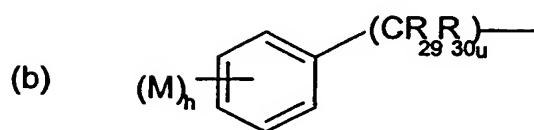
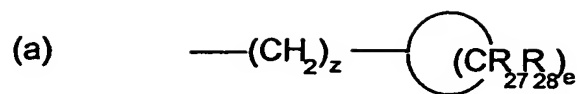
each R₂₅, and R₂₆ is independently hydrogen or C₁-C₆alkyl;

t is 0 or 1; and

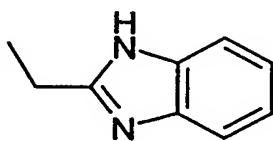
10

q is 0 or 1;

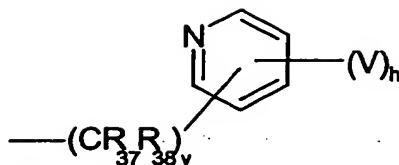
R₂ is a group selected from (a) – (n):



(f)

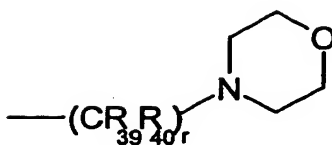


(g) -----



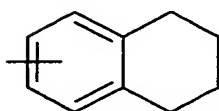
5

(h)



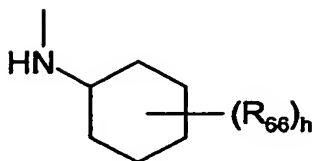
10

(i)



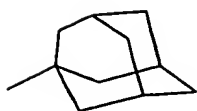
15

(j)



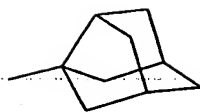
20

(k)



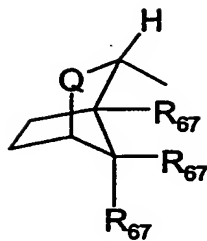
5

(l)



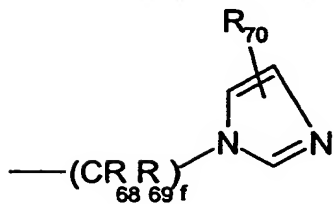
10

(m)



15

(n)



wherein

20

each R_{27} and R_{28} is independently selected from:

- (1) hydrogen;
- (2) C_1 - C_6 alkyl;
- (3) C_1 - C_6 alkoxy;
- (4) $-CO_2-R_{43}$ wherein R_{43} is hydrogen or

C₁-C₂alkyl;

(5) hydroxy;

(6) -(CH₂)-OR₄₄ wherein R₄₄ is hydrogen or C₁-C₂alkyl;

(7) -(CO)-NR₄₅R₄₆

wherein R₄₅ and R₄₆ are each independently hydrogen, C₁-C₂alkyl, or R₄₅ and R₄₆ taken together form a 5-membered monocyclic ring;

(8) -(CH₂)_a-OR₄₇ wherein R₄₇ is hydrogen or C₁-C₂alkyl and a is 1 or 2;

each M and V is a group independently selected from hydrogen, halogen, C₁-C₆alkyl, C₁-C₆alkoxy, trifluoromethyl, hydroxy, phenoxy or -NR₄₈R₄₉ wherein R₄₈ and R₄₉ are each independently hydrogen or C₁-C₂alkyl;

each R₂₉, R₃₀, R₃₁, R₃₂, R₃₃, R₃₄, R₃₅, R₃₆, R₃₇, R₃₈, R₃₉, R₄₀, R₆₈, and R₆₉ is independently hydrogen or C₁-C₆alkyl;

each R₆₃, R₆₄ and R₆₅ is independently hydrogen, halogen, C₁-C₆alkyl or C₁-C₆alkoxy;

each R₆₆ is independently hydrogen, hydroxy, C₁-C₆alkyl or C₁-C₆alkoxy;

Q is CH₂, CHOH or C=O;

each R₆₇ is independently hydrogen or C₁-C₆alkyl;

R₇₀ is hydrogen, C₁-C₆alkyl, halogen, or a phenyl group which is unsubstituted or mono-substituted with C₁-C₆alkyl, halogen or trifluoromethyl;

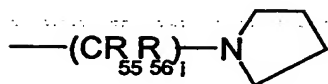
f is 1, 2, 3, or 4;

z is 0 or 1;
 u, j, l, o, r are 0 or 1;
 h is 0, 1, 2, or 3;
 e is 2, 3, 4, 5, or 7;
 v is 0, 1 or 2; and
 X is O or S;

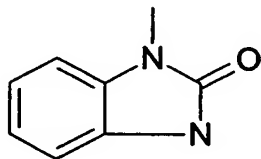
or R₁ and R₂ are joined together to form a 5-, 6-, or 7-membered monocyclic saturated ring, and in which the ring is unsubstituted or mono- or di-substituted, the substituents independently selected from:

- (1) C₁-C₆alkyl;
- (2) -CO₂-(C₁-C₂alkyl);
- (3) -NR₅₀R₅₁ wherein R₅₀ and R₅₁ are each independently C₁-C₆alkyl;
- (4) hydroxy;
- (5) -(CH₂)-OR₅₂ wherein R₅₂ is hydrogen or C₁-C₂alkyl;
- (6) -NR₅₄-COR₅₃ wherein R₅₄ is hydrogen or C₁-C₆alkyl and R₅₃ is hydrogen or C₁-C₂alkyl ;
- (7) =O;
- (8) -CN;

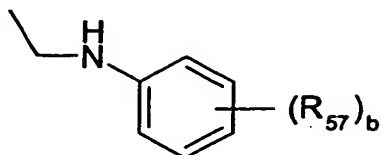
(9)



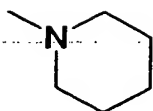
(10)



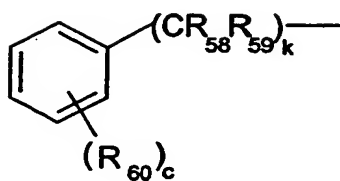
(11)



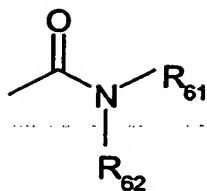
(12)



(13)



(14)



wherein

i is 0 or 1;

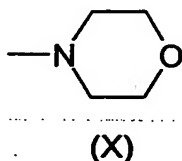
each R_{55} , R_{56} , R_{58} , and R_{59} is independently hydrogen or C_1 - C_6 alkyl;each R_{57} is independently hydrogen, halogen or C_1 - C_6 alkyl;each R_{60} is independently hydrogen, halogen or C_1 - C_6 alkyl; R_{61} and R_{62} are each independently hydrogen or C_1 - C_6 alkyl;

k is 0 or 1;

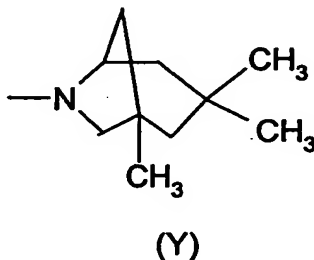
b and c are 0, 1 or 2;

or R₁ and R₂ are joined together to form a group of formula X;

5

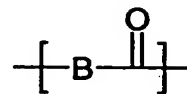


or R₁ and R₂ are joined together to form the group of formula (Y)



10

with the proviso that when n is 2, R₃ is hydrogen or C₁-C₆alkyl, group (a), and R is group:



is

15

(a) wherein R₄ is hydrogen, halogen or C₁-C₆alkyl, and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

(a) wherein z is 0,

(b) wherein u is 0 and M is hydrogen, halogen, C₁-C₆alkyl, or trifluoromethyl,

(c) wherein o is 0,

20

(d) wherein l is 0,

(e) wherein j is 0,

(g) wherein v is 0, or

(i);

25

and also when R is the group of formula (a), R₁ and R₂ cannot be joined together to form the group of formula Y or a 5-, 6-, or 7-membered monocyclic

ring wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl;

(b) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

(a),

(b),

(c) wherein o is 0,

(d) wherein l is 0,

(i),

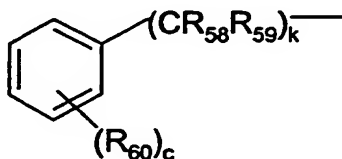
(k),

(l), or

(m) wherein Q is CH₂;

and also when R is the group of formula (b), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or



(c) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

(c) wherein o is 0,

(d) wherein l is 0, or

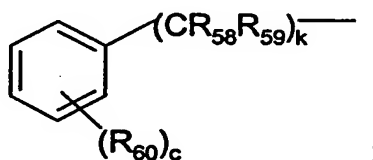
(i);

(d) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
- (b) wherein u is 1,
- (c) wherein o is 0,
- (d),
- (i),
- (k),
- (l), or
- (m) wherein Q is CH_2 ;

and also when R is the group of formula (d), R_1 and R_2 cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl or

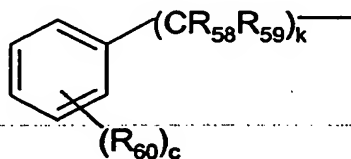


(e) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
- (b),
- (c) wherein o is 0,
- (d),
- (i),
- (k),
- (l), or
- (m) wherein Q is CH_2 ;

and also when R is the group of formula (e), R_1 and R_2 cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl or

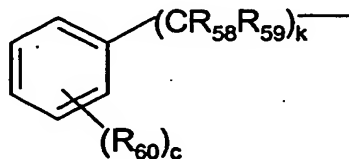


(f) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
- (b),
- (c) wherein o is 0,
- (d),
- (i),
- (k),
- (l), or
- (m) wherein Q is CH_2 ;

and also when R is the group of formula (f), R_1 and R_2 cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl or



(g) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
- (b) wherein u is 1,

(c) wherein o is 0,

(d),

(i),

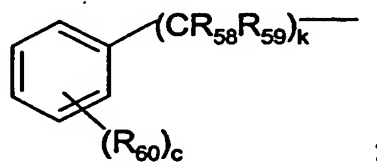
(k),

(l), or

(m) wherein Q is CH₂;

and also when R is the group of formula (g), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or



(h) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

(a),

(b),

(c) wherein o is 0,

(d),

(i),

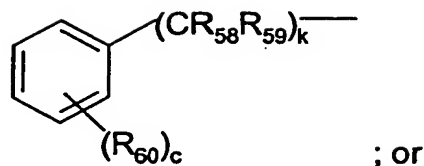
(k),

(l), or

(m) wherein Q is CH₂;

and also when R is the group of formula (h), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or

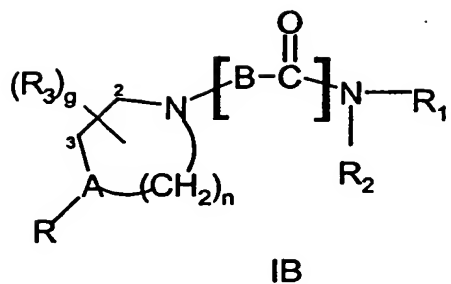


- 5 (j), then R_1 and R_2 cannot be joined together to form a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl.

- 10 2. The compound of claim 1 wherein R is group (a).
 3. The compound of claim 2 wherein R_4 is halogen or CF_3 .
 4. The compound of claim 3 wherein R_2 is group (a).
 5. The compound of claim 4 wherein z is 0 or 1;
 e is 5 and each R_{27} and R_{28} is independently selected from hydrogen or C_1 - C_6 alkyl.
- 15 6. The compound of claim 3 wherein R_2 is group (b).
 7. The compound of claim 6 wherein M is hydrogen, C_1 - C_6 alkoxy or C_1 - C_6 alkyl and u is 0 or 1.
 8. The compound of claim 3 wherein R_2 is group (n).
 9. The compound of claim 8 wherein R_{70} is hydrogen and f is 3.
- 20 10. The compound of claim 1 wherein R is group (k).
 11. The compound of claim 10 wherein R_{12} is hydrogen, C_1 - C_6 alkyl, or $-CH_2OC_1$ - C_6 alkyl.
 12. The compound of claim 11 wherein R_2 is group (a).
 13. The compound of claim 12 wherein z is 0 or 1;
 e is 5 and each R_{27} and R_{28} is independently selected from hydrogen or C_1 - C_6 alkyl.
- 25 14. The compound of claim 11 wherein R_2 is group (b).
 15. The compound of claim 14 wherein M is hydrogen, C_1 - C_6 alkoxy or C_1 - C_6 alkyl and u is 0 or 1.
 16. The compound of claim 11 wherein R_2 is group (n).
 17. The compound of claim 17 wherein R_{70} is hydrogen and f is 3.
- 30 18. The compound of claim 1 which is 2-[4-(6-trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-*trans*-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide.

- 19 The compound of claim 1 which is 2-[4-(2,4-dimethyl-phenyl)-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide.
20. The compound of claim 1 which is 2-[4-(chloro-trifluoromethyl-pyridin-2-yl)-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide.
21. The compound of claim 1 which is 2-[4-(2,5-dimethyl-phenyl)-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide.
22. The compound of claim 1 which is 2-[4-(6-trifluoromethyl-benzo[b]thiophen-3-yl)-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-methyl-cyclohexyl)-amide.
23. The compound of claim 1 which is 2-(4-thieno[2,3-*d*]isoxazol-3-yl-piperidin-1-ylmethyl)-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-methyl-cyclohexyl)-amide.
24. The compound of claim 1 which is 2-[4-*o*-tolyl-piperazin-1-ylmethyl]-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-ethyl-cyclohexyl)-amide.
25. The compound of claim 1 which is 4-[4-(6-fluoro-benzo[b]thiophen-3-yl)-piperazin-1-yl]-*N*-(*trans*-4-methyl-cyclohexyl)-butyramide.
26. The compound of claim 1 which is 2-(4-thieno[2,3-*d*]isoxazol-3-yl-piperidin-1-ylmethyl)-(2R, 3R)-cyclopropanecarboxylic acid (3-imidazol-1-yl-propyl)-amide.
27. The compound of claim 1 which is 2-(4-thieno[2,3-*d*]isoxazol-3-yl-piperazin-1-ylmethyl)-(2R, 3R)-cyclopropanecarboxylic acid (*trans*-4-methyl-cyclohexyl)-amide.
28. A method of modulating the activity of dopamine D₃ receptors, said method comprising: contacting cell-associated dopamine D₃ receptors with a concentration of a compound of formula IB, or a physiologically acceptable salt thereof, sufficient to modulate the activity of said dopamine D₃ receptor wherein said compound of formula IB has the structure:



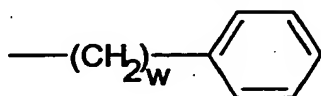
wherein

A is CH or N;

n is 2 or 3;

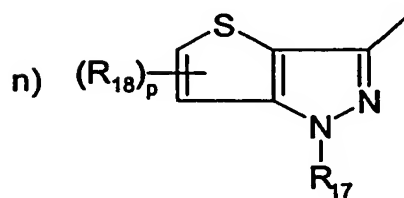
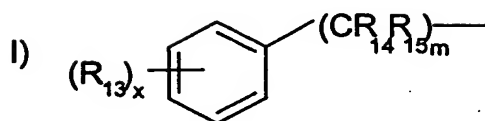
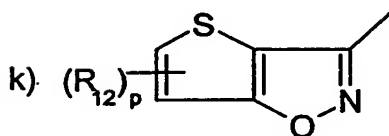
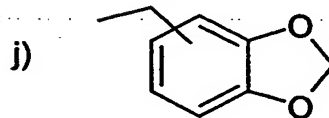
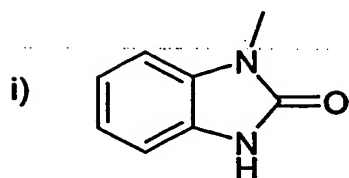
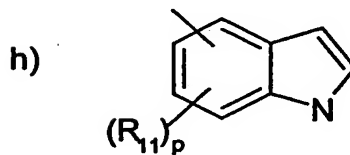
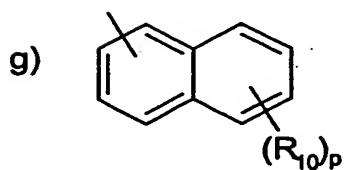
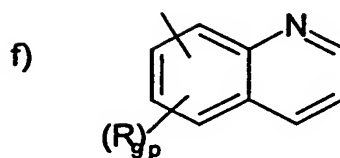
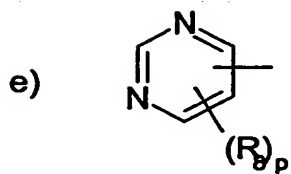
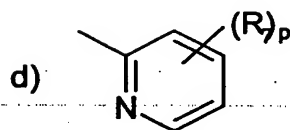
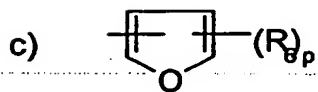
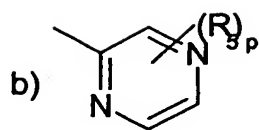
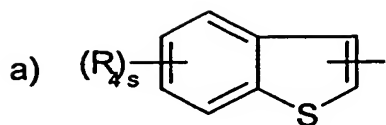
g is 1 or 2;

each R₃ is independently hydrogen, C₁-C₆alkyl, or



wherein w is 1, 2, or 3;

R is selected from the group consisting of (a) - (n):



wherein

5 each $R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}$ and R_{18} is independently hydrogen, C_1-C_6 alkyl, halogen, trifluoromethyl or $-CH_2OC_1-C_6$ alkyl;

p, s and x are 0, 1, or 2;

each R_{13} is independently hydrogen, C_1-C_6 alkyl, halogen, trifluoromethyl, C_1-C_6 alkoxy, nitro, CN , or COC_1-C_6 alkyl;

10 R_{16} is C_1-C_6 alkyl;

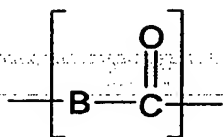
each R_{14} and R_{15} is independently hydrogen or C_1-C_6 alkyl;

R_{17} is hydrogen, C_1-C_6 alkyl, Ar, $-COAr$, $-CONHAr$ or $-SO_2Ar$ wherein

Ar is a phenyl group which is unsubstituted or mono- or di-substituted with substituents independently selected from C_1-C_6 alkyl, halogen, trifluoromethyl, C_1-C_6 alkoxy, nitro, CN and COC_1-C_6 alkyl; and

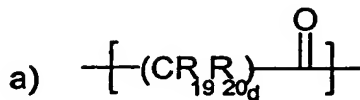
15

m is 0, 1, or 2;



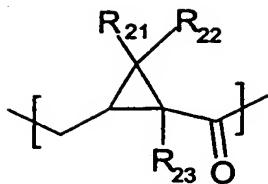
represents a group selected from (a) - (e):

20

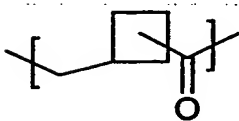


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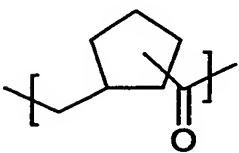
b)



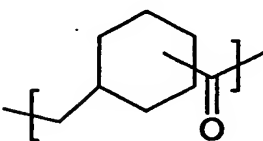
(c)



(d)



(e)



wherein

each R_{19} and R_{20} is independently hydrogen, hydroxy or C_1 - C_6 alkyl;

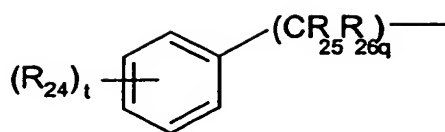
R_{21} , R_{22} , and R_{23} are each independently hydrogen or C_1 - C_3 linear alkyl; and

d is 3 or 4;

R_1 is a) hydrogen;

b) C_1 - C_6 alkyl, unsubstituted or mono- or di-substituted with hydroxy; or

c)



wherein

each R_{24} is independently hydrogen or C_1 - C_6 alkyl;

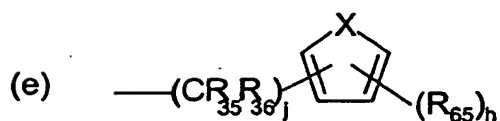
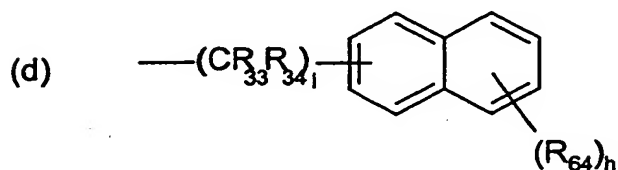
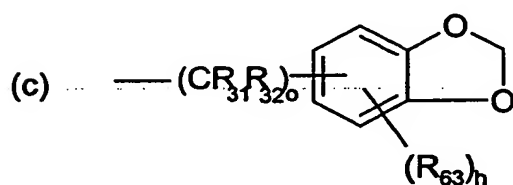
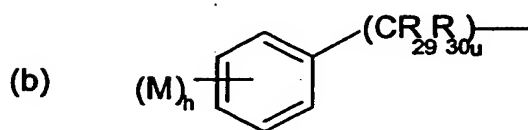
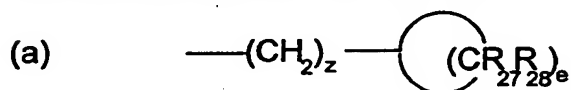
each R_{25} , and R_{26} is independently hydrogen or

C_1 - C_6 alkyl;

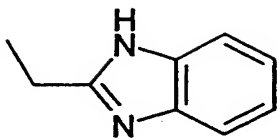
t is 0 or 1; and

q is 0 or 1;

R_2 is a group selected from (a) - (e):



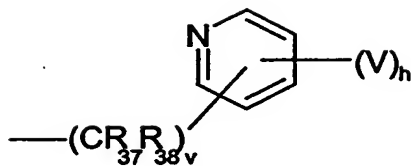
(f)



5

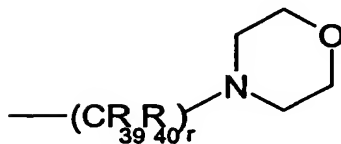
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(g)



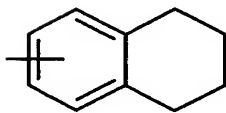
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(h)



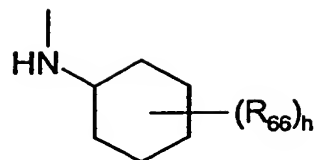
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(i)



(j)

A 4015



5 (k)



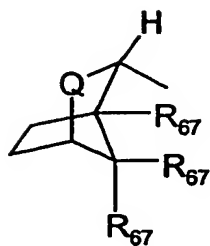
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(l)



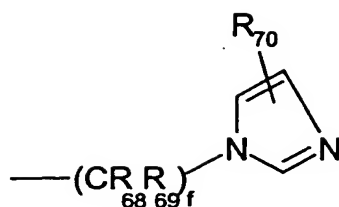
15

(m)



20

(n)



wherein

5 each R_{27} and R_{28} is independently selected from:

- (1) hydrogen;
- (2) $\text{C}_1\text{-C}_6$ alkyl;
- (3) $\text{C}_1\text{-C}_6$ alkoxy;
- (4) $-\text{CO}_2\text{-R}_{43}$ wherein R_{43} is hydrogen or $\text{C}_1\text{-C}_2$ alkyl;
- (5) hydroxy;
- (6) $-(\text{CH}_2)\text{-OR}_{44}$ wherein R_{44} is hydrogen or $\text{C}_1\text{-C}_2$ alkyl;
- (7) $-(\text{CO})\text{-NR}_{45}\text{R}_{46}$

15 wherein R_{45} and R_{46} are each independently hydrogen, $\text{C}_1\text{-C}_2$ alkyl, or R_{45} and R_{46} taken together form a 5-membered monocyclic ring;

- (8) $-(\text{CH}_2)_a\text{-OR}_{47}$ wherein R_{47} is hydrogen or $\text{C}_1\text{-C}_2$ alkyl and a is 1 or 2;

20 each M and V is a group independently selected from hydrogen, halogen, $\text{C}_1\text{-C}_6$ alkyl, $\text{C}_1\text{-C}_6$ alkoxy, trifluoromethyl, hydroxy, phenoxy or $-\text{NR}_{48}\text{R}_{49}$ wherein R_{48} and R_{49} are each independently hydrogen or $\text{C}_1\text{-C}_2$ alkyl;

25 each R_{29} , R_{30} , R_{31} , R_{32} , R_{33} , R_{34} , R_{35} , R_{36} , R_{37} , R_{38} , R_{39} , R_{40} , R_{68} , and R_{69} is independently hydrogen or $\text{C}_1\text{-C}_6$ alkyl;
 each R_{63} , R_{64} and R_{65} is independently hydrogen, halogen, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ alkoxy;
 30 each R_{66} is independently hydrogen, hydroxy, $\text{C}_1\text{-C}_6$ alkyl or $\text{C}_1\text{-C}_6$ alkoxy;

Q is CH₂, CHOH or C=O;

each R₆₇ is independently hydrogen or C₁-C₆alkyl;

R₇₀ is hydrogen, C₁-C₆alkyl, halogen, or a phenyl group which is unsubstituted or mono-substituted with C₁-C₆alkyl, halogen or trifluoromethyl;

f is 1, 2, 3, or 4;

z is 0 or 1;

u, j, l, o, r are 0 or 1;

h is 0, 1, 2, or 3;

e is 2, 3, 4, 5, or 7;

v is 0, 1 or 2; and

X is O or S;

or R₁ and R₂ are joined together to form a 5-, 6-, or 7-membered monocyclic saturated ring, and in which the ring is unsubstituted or mono- or di-substituted, the substituents independently selected from:

(1) C₁-C₈alkyl;

(2) -CO₂-(C₁-C₂alkyl);

(3) -NR₅₀R₅₁ wherein R₅₀ and R₅₁ are each independently C₁-C₆alkyl;

(4) hydroxy;

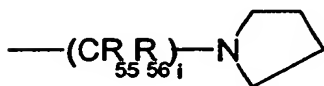
(5) -(CH₂)-OR₅₂ wherein R₅₂ is hydrogen or C₁-C₂alkyl;

(6) -NR₅₄-COR₅₃ wherein R₅₄ is hydrogen or C₁-C₆alkyl and R₅₃ is hydrogen or C₁-C₂alkyl ;

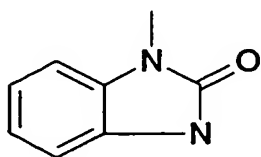
(7) =O;

(8) -CN;

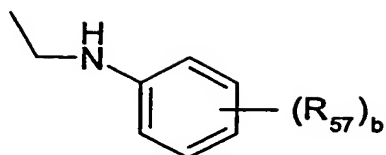
(9)



(10)

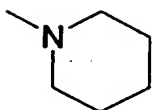


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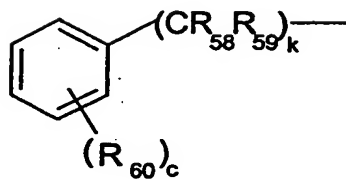
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(12)



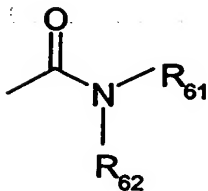
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(13)



15

(14)



wherein

20

i is 0 or 1;

each R_{55} , R_{56} , R_{58} , and R_{59} is independently hydrogen or C_1 - C_6 alkyl;each R_{57} is independently hydrogen, halogen or C_1 - C_6 alkyl;

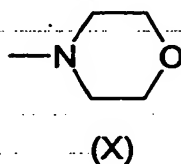
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each R_{60} is independently hydrogen, halogen or C_1 - C_6 alkyl;

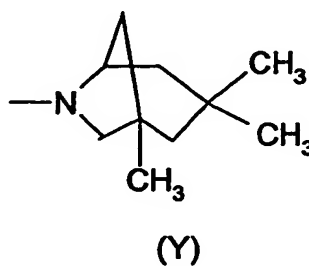
R_{61} and R_{62} are each independently hydrogen or C_1 - C_6 alkyl;
 k is 0 or 1;
 b and c are 0, 1 or 2;

5

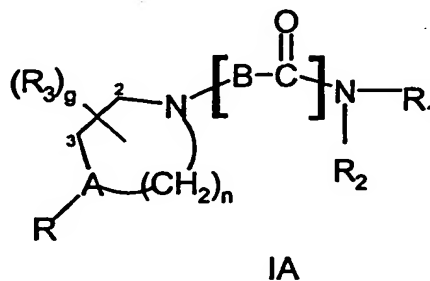
or R_1 and R_2 are joined together to form a group of formula X;



10 or R_1 and R_2 are joined together to form the group of formula (Y)



- 15 29. A method of treating conditions or disorders of the central nervous system comprising administering to a patient in need thereof a therapeutically effective amount of a compound of formula IA, or a pharmaceutically acceptable salt thereof wherein said compound of formula IA has the structure:



20

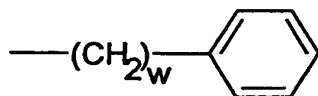
wherein

A is CH or N;

n is 2 or 3;

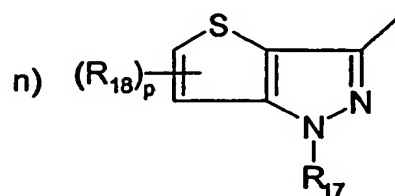
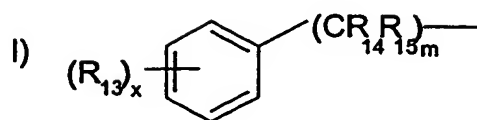
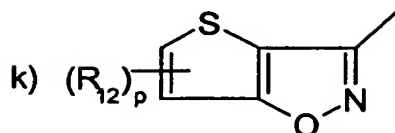
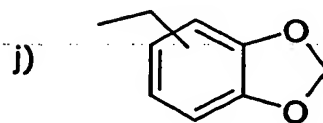
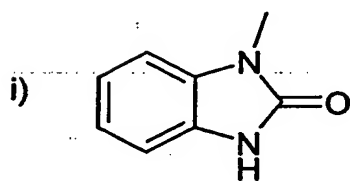
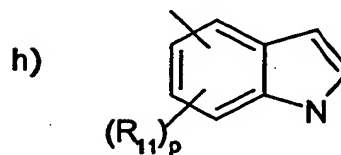
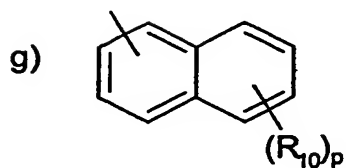
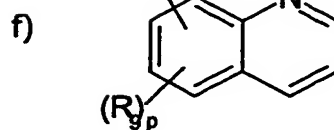
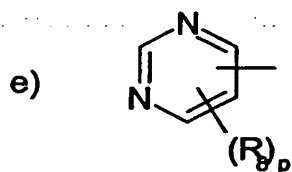
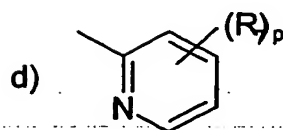
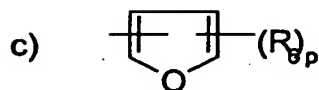
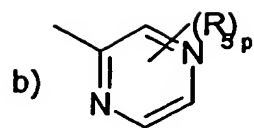
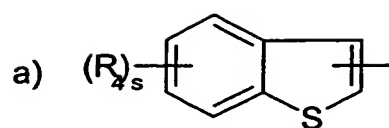
g is 1 or 2;

each R_3 is independently hydrogen, C_1 - C_6 alkyl, or



wherein w is 1, 2, or 3;

R is selected from the group consisting of (a) – (n):



wherein

5 each $R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}$ and R_{18} is independently hydrogen, C_1 - C_6 alkyl, halogen, trifluoromethyl or $-CH_2OC_1$ - C_6 alkyl ;
 p, s and x are 0, 1, or 2;

each R_{13} is independently hydrogen, C_1 - C_6 alkyl, halogen, trifluoromethyl, C_1 - C_6 alkoxy, nitro, CN, or COC_1 - C_6 alkyl;

10 R_{16} is C_1 - C_6 alkyl;

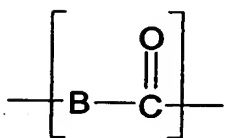
each R_{14} and R_{15} is independently hydrogen or C_1 - C_6 alkyl;

R_{17} is hydrogen, C_1 - C_6 alkyl, Ar, $-COAr$, $-CONHAr$ or $-SO_2$ -Ar wherein

Ar is a phenyl group which is unsubstituted or mono- or di-substituted with substituents independently selected from C_1 - C_6 alkyl, halogen, trifluoromethyl, C_1 - C_6 alkoxy, nitro, CN and COC_1 - C_6 alkyl; and

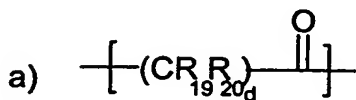
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m is 0, 1, or 2;



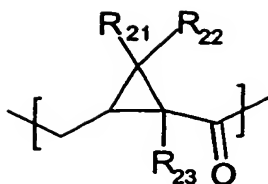
represents a group selected from (a) - (e):

20

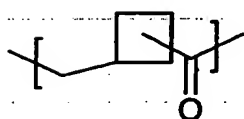


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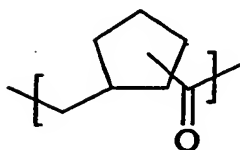
b)



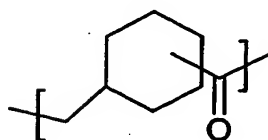
(c)



(d)



(e)



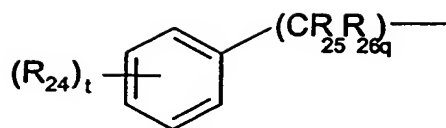
wherein

each R_{19} and R_{20} is independently hydrogen, hydroxy or C_1 - C_6 alkyl;

R_{21} , R_{22} , and R_{23} are each independently hydrogen or C_1 - C_3 linear alkyl; and

d is 3 or 4;

R_1 is a) hydrogen;
b) C_1 - C_6 alkyl, unsubstituted or mono- or di-substituted with hydroxy; or
c)



wherein

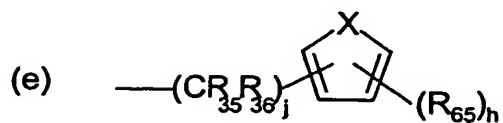
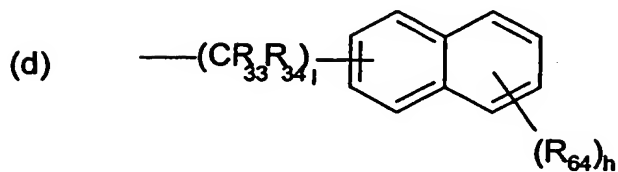
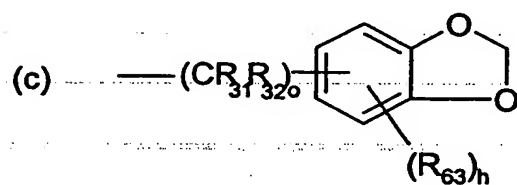
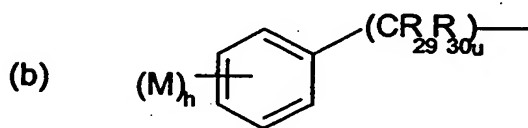
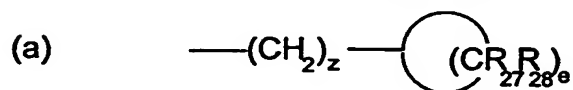
each R_{24} is independently hydrogen or C_1 - C_6 alkyl;

each R_{25} , and R_{26} is independently hydrogen or C_1 - C_6 alkyl;

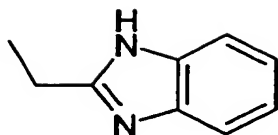
t is 0 or 1; and

q is 0 or 1;

R_2 is a group selected from (a) - (e):



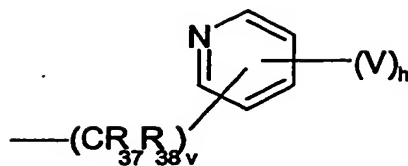
(f)



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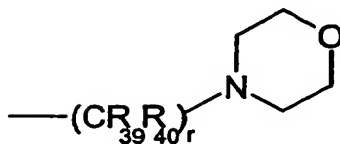
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(g)



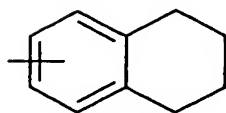
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(h)

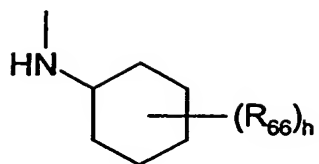


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(i)

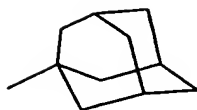


(j)



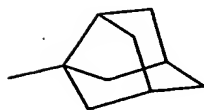
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(k)



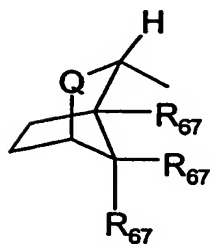
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(l)



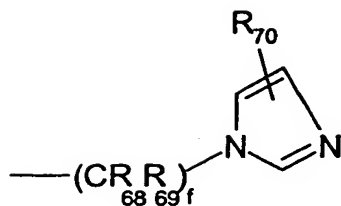
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(m)



20

(n)



wherein

each R_{27} and R_{28} is independently selected from:

- (1) hydrogen;
- (2) C_1 - C_6 alkyl;
- (3) C_1 - C_6 alkoxy;
- (4) $-CO_2R_{43}$ wherein R_{43} is hydrogen or C_1 - C_2 alkyl;
- (5) hydroxy;
- (6) $-(CH_2)-OR_{44}$ wherein R_{44} is hydrogen or C_1 - C_2 alkyl;
- (7) $-(CO)NR_{45}R_{46}$

wherein R_{45} and R_{46} are each independently hydrogen, C_1 - C_2 alkyl, or R_{45} and R_{46} taken together form a 5-membered monocyclic ring;

- (8) $-(CH_2)_a-OR_{47}$ wherein R_{47} is hydrogen or C_1 - C_2 alkyl and a is 1 or 2;

each M and V is a group independently selected from hydrogen, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, trifluoromethyl, hydroxy, phenoxy or $-NR_{48}R_{49}$ wherein R_{48} and R_{49} are each independently hydrogen or C_1 - C_2 alkyl;

each R_{29} , R_{30} , R_{31} , R_{32} , R_{33} , R_{34} , R_{35} , R_{36} , R_{37} , R_{38} , R_{39} , R_{40} , R_{88} , and R_{69} is independently hydrogen or C_1 - C_6 alkyl;

each R_{63} , R_{64} and R_{65} is independently hydrogen, halogen, C_1 - C_6 alkyl or C_1 - C_6 alkoxy;

each R_{66} is independently hydrogen, hydroxy, C_1 - C_6 alkyl or C_1 - C_6 alkoxy;

Q is CH₂, CHOH or C=O;

each R₆₇ is independently hydrogen or C₁-C₆alkyl;

R₇₀ is hydrogen, C₁-C₆alkyl, halogen, or a phenyl group which is unsubstituted or mono-substituted with C₁-C₆alkyl, halogen or trifluoromethyl;

f is 1, 2, 3, or 4;

z is 0 or 1;

u, j, l, o, r are 0 or 1;

h is 0, 1, 2, or 3;

e is 2, 3, 4, 5, or 7;

v is 0, 1 or 2; and

X is O or S;

or R₁ and R₂ are joined together to form a 5-, 6-, or 7-membered monocyclic saturated ring, and in which the ring is unsubstituted or mono- or di-substituted, the substituents independently selected from:

(1) C₁-C₆alkyl;

(2) -CO₂(C₁-C₂alkyl);

(3) -NR₅₀R₅₁ wherein R₅₀ and R₅₁ are each independently C₁-C₆alkyl;

(4) hydroxy;

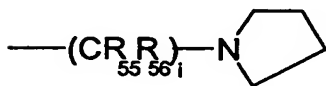
(5) -(CH₂)-OR₅₂ wherein R₅₂ is hydrogen or C₁-C₂alkyl;

(6) -NR₅₄-COR₅₃ wherein R₅₄ is hydrogen or C₁-C₆alkyl and R₅₃ is hydrogen or C₁-C₂alkyl ;

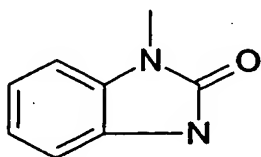
(7) =O;

(8) -CN;

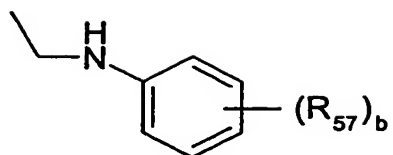
(9)



(10)

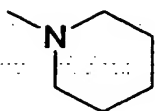


(11)



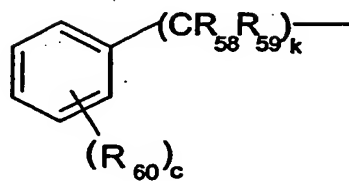
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(12)



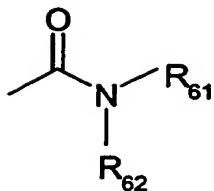
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(13)



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(14)



20

wherein

i is 0 or 1;

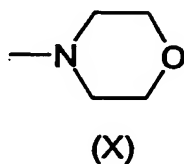
each R_{55} , R_{56} , R_{58} , and R_{59} is independently hydrogen or C_1 - C_6 alkyl;

25 each R_{57} is independently hydrogen, halogen or C_1 - C_6 alkyl;

each R_{60} is independently hydrogen, halogen or C_1 - C_6 alkyl;
 R_{61} and R_{62} are each independently hydrogen or C_1 - C_6 alkyl;
 k is 0 or 1;
 b and c are 0, 1 or 2;

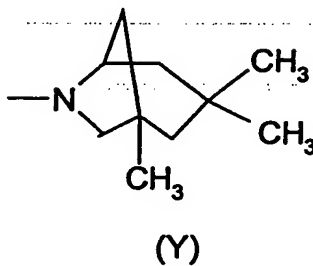
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or R_1 and R_2 are joined together to form a group of formula X;



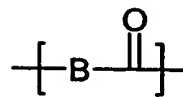
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or R_1 and R_2 are joined together to form the group of formula (Y)



20

with the proviso that when n is 2, R_3 is hydrogen or C_1 - C_6 alkyl,
 and R is group:



is group (a),

(a) wherein R_4 is hydrogen, halogen or C_1 - C_6 alkyl, and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

25

- (a) wherein z is 0,
 (b) wherein u is 0 and M is hydrogen, halogen, C_1 - C_6 alkyl, or trifluoromethyl,
 (c) wherein o is 0,
 (d) wherein l is 0,
 (e) wherein j is 0,
 (g) wherein v is 0, or
 (i);

and also when R is the group of formula (a), R_1 and R_2 cannot be joined together to form the group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

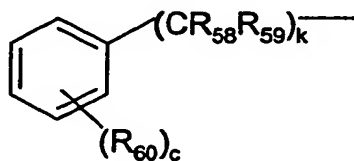
wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl;

(b) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
 (b),
 (d) wherein l is 0,
 (k),
 (l), or
 (m) wherein Q is CH_2 ;

and also when R is the group of formula (b), R_1 and R_2 cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl or

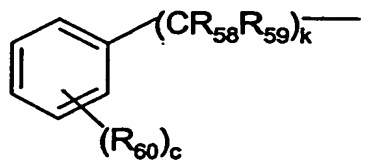


(d) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
- (b) wherein u is 1,
- (d),
- (k),
- (l), or
- (m) wherein Q is CH_2 ;

and also when R is the group of formula (d), R_1 and R_2 cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl or

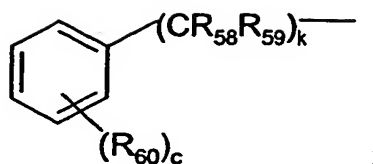


(e) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

- (a),
- (b),
- (d),
- (k),
- (l), or
- (m) wherein Q is CH_2 ;

and also when R is the group of formula (e), R_1 and R_2 cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl or



(f) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

(a),

(b),

(d),

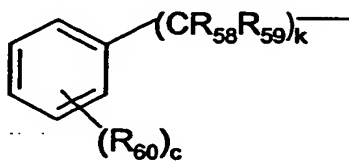
(k),

(l), or

(m) wherein Q is CH_2 ;

and also when R is the group of formula (f), R_1 and R_2 cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C_1 - C_6 alkyl or



(g) and R_1 is hydrogen or unsubstituted C_1 - C_6 alkyl, then R_2 cannot be a group of the following formula:

(a),

(b) wherein u is 1,

(d),

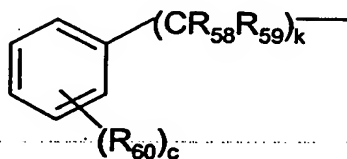
(k),

(l), or

(m) wherein Q is CH_2 ;

and also when R is the group of formula (g), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or

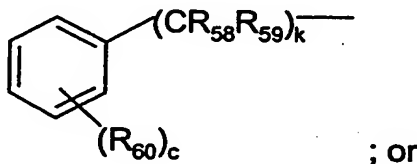


(h) and R₁ is hydrogen or unsubstituted C₁-C₆alkyl, then R₂ cannot be a group of the following formula:

- (a),
- (b),
- (d),
- (k),
- (l), or
- (m) wherein Q is CH₂;

and also when R is the group of formula (h), R₁ and R₂ cannot be joined together to form a group of formula X or a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl or



(j), then R₁ and R₂ cannot be joined together to form a group of formula Y or a 5-, 6-, or 7-membered monocyclic ring

wherein said ring is unsubstituted or mono- or di-substituted with C₁-C₆alkyl.

30. The method of claim 29, wherein the central nervous system disorder is selected from Psychotic Disorders, Substance Dependence, Substance Abuse, Dyskinetic Disorders, Dementia, Anxiety Disorders, Sleep Disorders, Circadian Rhythm Disorders, Mood Disorders and Nausea.
31. The method of claim 30 wherein the Psychotic Disorder is Schizophrenia.
32. The method of claim 29 wherein the compound of formula IB is administered in conjunction with one or more dopamine D₁, D₂, D₄, D₅, or 5HT receptor antagonists.
33. A pharmaceutical composition comprising an effective amount of a compound of claim 1 with a pharmaceutically-acceptable carrier or diluent.
34. A pharmaceutical composition comprising an effective amount of a compound of claim 1 with a pharmaceutically-acceptable carrier or diluent in conjunction with one or more dopamine D₁, D₂, D₄, D₅ or 5HT receptor antagonists.
35. A depot pharmaceutical composition, which comprises a pharmaceutically acceptable carrier and a therapeutically effective amount of the compound of claim 1, wherein the compound contains an acylated hydroxy group, or an acylated amino group.
36. The depot pharmaceutical composition of claim 35, wherein the hydroxy group is acylated, or the amino group is acylated with (C₄-C₁₈)alkanoyl group or a (C₄-C₁₈)alkoxycarbonyl group.
37. The composition of claim 35 which contains a pharmaceutically acceptable oil.
38. The composition of claim 37 wherein the oil is selected from the group consisting of coconut oil, peanut oil, sesame oil, cotton seed oil, corn oil, soybean oil, olive oil, and synthetic esters of fatty acids and polyfunctional alcohols.

39. A method for providing a long acting antipsychotic effect, which comprises injecting into a mammal an amount of the composition of claim 35 sufficient to produce a long acting antipsychotic effect.

5 40. A method for providing a long acting antipsychotic effect, which comprises injecting into a mammal an amount of the composition of claim 36 sufficient to produce a long acting antipsychotic effect.

10 41. A method for providing a long acting antipsychotic effect, which comprises injecting into a mammal an amount of the composition of claim 37 sufficient to produce a long acting antipsychotic effect.

42. A compound of claim 1 wherein one or more of the atoms contained therein is a radionuclide.

15

43. A compound of claim 42 wherein R is group (a), with a radiolabeled ^{14}C in the 3-position of the benzo[b]thiophene ring, R_4 is trifluoromethyl, s is 1, R_3 is hydrogen, n is 2 and A is N.

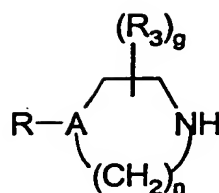
20 44. A diagnostic method for monitoring neuronal functions in a mammal comprising introducing into a mammal a radiolabeled compound according to claim 42.

25 45. The method of claim 44 wherein said diagnostic method is performed using single positron emission computed tomography.

46. A process for preparing a compound of formula I of claim 1 which comprises:

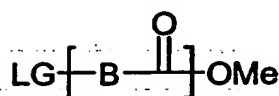
(a) reacting a compound of formula (II):

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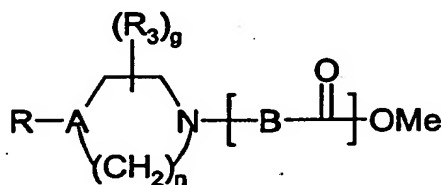
(II)

wherein R_3 , g , R , A and n are as defined in formula I of claim 1
with a compound of formula (III)



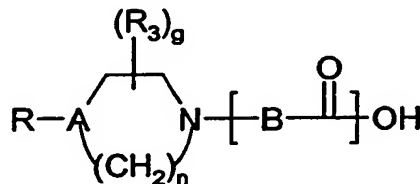
(III)

wherein "LG" is a suitable leaving group selected from chlorine, bromine, iodine and
mesyl and B is as defined in formula I of claim 1
to provide a compound of formula (IV)



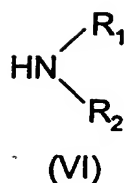
(IV)

(b) hydrolyzing a compound of formula (IV) to provide a compound of formula (V)



(V)

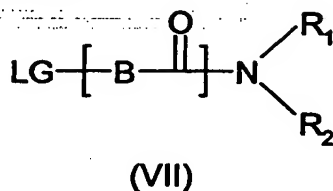
and (c) reacting a compound of formula (V) with a compound of formula (VI)



to provide a compound of formula (I).

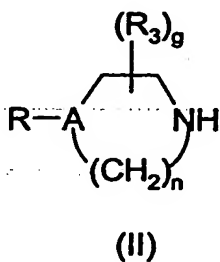
5 47. A process for preparing compounds of formula I of claim 1 which comprises:

(a) reacting a compound of formula (VII)



wherein "LG" is a suitable leaving group selected from chlorine, bromine, iodine and mesyl and B, R₁ and R₂ are as defined in formula I of claim 1

with a compound of formula (II)



15 wherein R₃, g, R, A and n are as defined in formula I of claim 1

to provide a compound of formula (I).

ABSTRACT

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The invention relates to heterocyclic substituted carbonyl derivatives that display selective binding to dopamine D₃ receptors. In another aspect, the invention relates to a method for treating central nervous system disorders associated with the dopamine D₃ receptor activity in a patient in need of such treatment comprising administering to the subject a therapeutically effective amount of said compounds for alleviation of such disorder. The central nervous system disorders that may be treated with these compounds include Psychotic Disorders, Substance Dependence, Substance Abuse, Dyskinetic Disorders (e.g. Parkinson's Disease, Parkinsonism, Neuroleptic-Induced Tardive Dyskinesia, Gilles de la Tourette Syndrome and Huntington's Disease), Dementia, Anxiety Disorders, Sleep Disorders, Circadian Rhythm Disorders and Mood Disorders. The subject invention is also directed towards processes for the preparation of the compounds described herein as well as methods for making and using the compounds as imaging agents for dopamine D₃ receptors.

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